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Topical medication instillation techniques for glaucoma (Review)

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[Intervention Review]

Topical medication instillation techniques for glaucoma

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ABSTRACT

Background

Glaucoma is a leading cause of irreversible blindness worldwide and the second most common cause of blindness after cataracts. The primary treatment for glaucoma aims to lower intraocular pressure (IOP) with the use of topical medicines. Topical medication instillation techniques, such as eyelid closure and nasolacrimal occlusion when instilling drops, have been proposed as potential methods to increase ocular absorption and decrease systemic absorption of the drops.

Objectives

To investigate the effectiveness of topical medication instillation techniques compared with usual care or another method of instillation of topical medication in the management of glaucoma or ocular hypertension.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 12), MEDLINE Ovid (1946 to 8 December 2016), Embase Ovid (1947 to 8 December 2016), PubMed (1948 to 8 December 2016), LILACS (Latin American and Caribbean Health Sciences Literature Database) (1982 to 8 December 2016), International Pharmaceutical Abstracts Database (1970 to 8 December 2016), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) (last searched 13 May 2013), ClinicalTrials.gov (www.clinicaltrials.gov) (searched 8 December 2016) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) (searched 8 December 2016). We did not use any date or language restrictions in the electronic searches for trials.

Selection criteria

We included randomized controlled trials which had compared any topical medication instillation technique with usual care or a different method of instillation of topical medication.

Data collection and analysis

Two review authors independently screened records from the searches for eligibility, assessed the risk of bias, and extracted data. We followed methods recommended by Cochrane.

Main results

We identified two trials (122 eyes of 61 participants) that had evaluated a topical medication instillation technique. We also identified two ongoing trials. Both included trials used a within-person design and administered prostaglandin monotherapy for glaucoma or ocular

hypertension. Because the trials evaluated different instillation techniques and assessed different outcomes, we performed no meta-analysis.

One trial, conducted in the US, evaluated the effect of eyelid closure (one and three minutes) versus no eyelid closure on lowering IOP. At one to two weeks' follow-up, reduction in IOP was similar in the eyelid closure group and the no eyelid closure group (mean difference (MD) -0.33 mmHg, 95% confidence interval (CI) -0.8 to 1.5; 51 participants; moderate-certainty evidence).

The second trial, conducted in Italy, evaluated the effect of using an absorbent cloth to wipe excess fluid after instillation (fluid removal) versus not using an absorbent cloth (no removal) on reducing dermatologic adverse events. At four months' follow-up, eyelashes were shorter among eyes in the fluid removal group compared with the no fluid removal group (MD -1.70 mm, 95% CI -3.46 to 0.06; 10 participants; low-certainty evidence). Fewer eyes showed skin hyperpigmentation in the eyelid region towards the nose in the fluid removal group compared with the no removal group (RR 0.07, 95% CI 0.01 to 0.84; 10 participants; low-certainty evidence); however, the difference was uncertain in the eyelid region towards the temples (RR 0.44, 95% CI 0.07 to 2.66; 10 participants; low-certainty evidence). The effect hypertrichosis (excessive hair growth) was uncertain between groups (RR 1.00, 95% CI 0.17 to 5.98; 10 participants; low-certainty evidence).

Neither trial reported other outcomes specified for this review, including the proportion of participants with IOP less than 21 mmHg; participant-reported outcomes related to the ease, convenience, and comfort of instillation techniques; physiologic measurements of systemic absorption; escalation of therapy; mean change in visual fields; optic nerve progression; mean change in best-corrected visual acuity; proportion in whom glaucoma developed; quality of life outcomes; or cost-effectiveness outcomes. Neither trial reported data at follow-up times of more than four months.

Authors' conclusions

Evidence to evaluate the effectiveness of topical medication instillation techniques for treatment of glaucoma is lacking. It is unclear what, if any, effects instillation techniques have on topical medical therapy for glaucoma.

PLAIN LANGUAGE SUMMARY

Topical medicine instillation techniques for glaucoma

What is the aim of this review?
The aim of this Cochrane Review was to find out if the way that people with glaucoma put eye drops in makes a difference in how well the eye drops work. Cochrane researchers collected and analyzed all relevant studies to answer this question and found two studies.

Key messages
It is unclear if the way that people with glaucoma put their eye drops in makes a difference in how well the drops work.

What did this review study?
Glaucoma is a leading cause of blindness worldwide. In eyes with glaucoma, the ability to see may be lost because of damage to the optic nerve. The optic nerve is the part of the eye that sends visual information from the eye to the brain. Sometimes such damage occurs when there is too much pressure in the eye (called intraocular pressure or IOP). Sometimes eyes may have too much pressure without damage to the optic nerve (called ocular hypertension). The main goal of glaucoma and ocular hypertension treatment is to lower IOP. Topical medicines, such as eye drops, are most often used as the first treatment. Encouraging specific ways of applying the drops, such as closing your eyes or nasolacrimal occlusion (closing the eye and pressing a finger on the inside corner, by the nose) aims to increase how much medicine is absorbed into the eye and reduce how much medicine is absorbed into the body.

What are the main results of the review?
We found two studies that compared different ways of putting in eye drops. Both studies used prostaglandin alone for glaucoma or ocular hypertension. One study, in the US, evaluated the effect of closing the eyes for one and three minutes after putting in eye drops on lowering IOP. The second study, in Italy, looked at whether wiping off the excess fluid, after putting in the eye drops, led to fewer changes in the skin surrounding the eye.

After one to two weeks in the US study, closing the eyelid for one to three minutes after putting in the eye drops found no difference on IOP compared with not closing the eyelid for a specified amount of time. After four months in the Italian study, eyelashes were shorter when participants had wiped their eyes to remove excess fluid when compared with participants who did not wipe their eyes.

We found two ongoing studies that do not have results yet.

Based on only two studies and uncertain results, it is unclear if different ways of putting in eye drops have any effect on people with glaucoma.

How up-to-date is this review?
Cochrane researchers searched for studies that had been published up to 8 December 2016.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Topical medication instillation techniques for glaucoma

Topical medication instillation techniques for glaucoma

Population: participants with glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: any intervention aimed to increase effectiveness or reduce adverse events when using topical medications (e.g. eyelid closure, nasolacrimal occlusion, removal of excess fluid after instillation)

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Instillation intervention				
Proportion of participants with IOP < 21 mmHg at 1 year' follow-up	Not reported					-
Mean IOP change from baseline at 1 year' follow-up	Not reported					1 trial reported that reduction of IOP was similar in eyes when the eyelid was kept closed for up to 3 minutes after instillation of drops than fellow eyes that did not practice eyelid closure at 2 weeks (MD -0.33 mmHg, 95% CI -0.8 to 1.5; 51 participants); moderate-certainty evidence.[1]
Participant-reported outcomes related to the ease, convenience, and comfort of instillation at 1 year' follow-up	Not reported					-

Physiologic measurements of systemic absorption at 1 year' follow-up	Not reported	-
Escalation of therapy at 1 year' follow-up	Not reported	-
Mean change in visual fields at 1 year' follow-up	Not reported	-
Adverse events at 1 year' follow-up	Not reported	1 trial with up to 4 months' follow-up reported that eyelashes were shorter among eyes when participants had wiped to remove excess fluid compared with fellow eyes that were not wiped (MD -1.70 mm, 95% CI -3.46 to 0.06; 10 participants) and fewer eyes had eyelash growth of > 1.5 mm when wiping compared with not wiping (RR 0.11, 95% CI 0.01 to 1.24); low-certainty evidence.[1,2] This same trial also reported that fewer eyes showed skin hyperpigmentation in the eyelid region towards the nose when wiping compared with not wiping (RR 0.07, 95% CI 0.01 to 0.84); however, the difference was not certain when assessing skin hyperpigmentation in the eyelid region towards the temples (RR 0.44, 95% CI 0.07 to 2.66) or hair growth on the skin around the eye (RR 1.00, 95% CI 0.17 to 5.98); low-certainty evidence.[1,2]

*The basis for the **assumed risk** is the risk in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IOP:** intraocular pressure; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence
High-certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: We are very uncertain about the estimate.

[1]Downgraded one level for risk of performance, detection bias, or both.
[2]Downgraded one level for imprecision.

BACKGROUND

Description of the condition

Glaucoma is a chronic, progressive optic neuropathy. If left undiagnosed and untreated, the optic nerve of people with glaucoma may sustain irreversible damage (Lee 2005). At the end stage, people have permanent visual field loss and blindness (Marquis 2005).

Factors associated with increased risk for the development of glaucoma include elevated intraocular pressure (IOP), increasing age, a positive family history of glaucoma, African or Asian racial background, near-sightedness, and thinner central corneal thickness (Alsbirk 1976; Armaly 1980; Coleman 2008; Ernest 2013; Landers 2002; Le 2003; Medeiros 2003; Tielsch 1996). Elevated IOP is viewed as a major risk factor of glaucoma rather than a defining feature of the condition because elevated IOP and glaucomatous optic neuropathy (GON) do not necessarily coexist (Casson 2012). Additionally, IOP is the only known risk factor that can be modified.

Epidemiology of glaucoma

Glaucoma is a significant public health problem as it is the leading cause of irreversible blindness worldwide and the second most common cause of blindness after cataracts (Heijl 2009; Pan 2011; Quigley 1996). In 2014, Tham and colleagues estimated that 3.54% of people in the world between the ages of 40 to 80 years had glaucoma and projected that the worldwide prevalence of glaucoma would be 76.0 million in 2020 and 111.8 million people in 2040 (Tham 2014). An earlier study projected the number of people bilaterally blind from primary glaucoma would to be more than 11.2 million by 2020 (Quigley 2006). In the US, 10% of people who are bilaterally blind are believed to be blind secondary to glaucoma (Congdon 2004). Primary open-angle glaucoma (POAG) is the most common type of glaucoma, accounting for 74% of all persons with glaucoma (Quigley 1996).

Glaucoma treatment

Because no treatment has been proven to repair or regenerate a damaged optic nerve, the primary purpose of glaucoma therapy is to manage IOP to a target level at which progressive GON and vision loss are stopped or delayed (Lee 2005). IOP reduction is the only current evidence-based treatment strategy for all types of glaucoma, including normal tension glaucoma (Casson 2012). In general, three main treatments for glaucoma are directed toward reducing IOP: medical therapy, laser therapy, and incisional surgery. Although each of these types of treatments is effective in lowering IOP to some extent, therapy usually begins with medications. To reduce IOP further to a target level, medications can be used as supplemental treatment with laser or surgery when laser or surgery alone is not successful in reaching the target postoperative IOP.

The mechanics of medications in lowering IOP involve reducing aqueous humor production or increasing the rate of outflow of aqueous humor within the eye. For most people, one or more topical medications are effective in reducing IOP. Many medical treatments, usually applied topically, are available for this purpose (e.g. prostaglandin analogs, beta-blockers, alpha2-selective adrenergic agonists, cholinergic agonists, and carbonic anhydrase inhibitors) (Noecker 2006).

Description of the intervention

Many topical antiglaucoma medications are associated with systemic adverse events. For example, beta-blockers have been associated with arrhythmias, congestive cardiac failure, and airway obstruction (Ehongo 2007); and carbonic anhydrase inhibitors may cause thrombocytopenia (Beckers 2008; Cantor 1989). There also are concerns related to local side effects. For example, prostaglandins have been associated with undesired eye lash growth, pigmentation of the iris (colored part of the eye), and darkening of skin around the eyes (Smith 2012). To increase the therapeutic index of antiglaucoma medications (i.e. to increase the desired therapeutic effect while reducing the undesired adverse events), various techniques for applying medications topically have been suggested (Zimmerman 1984). Examples of topical medication instillation techniques include eyelid closure (ELC), nasolacrimal (tear drainage) occlusion (NLO), changes in the proximity of the eye-dropper tip to the eyes (contact versus no contact), instillation of drops into the conjunctival sac, removal of excess fluid after instillation, and delayed time interval between instillation of multiple topical medications. These techniques are designed to improve ocular bioavailability and to lower systemic absorption of the drug during instillation of topical medications to achieve the goal of increasing the therapeutic index (Bourlais 1998; Shell 1984; Zimmerman 1983). ELC involves gently closing the eyes for several minutes after the medication is applied, to prolong eye-drug contact and to block drainage of the drug into the nasopharyngeal mucosa. NLO is achieved by applying pressure over the area between the bridge of the nose and the inner canthus, known as the periphery of the nasolacrimal drainage system, to block tear drainage.

How the intervention might work

When ocular medications are instilled topically, some medication may spill out of the eye or may not be completely absorbed by the target area. Some studies have suggested that as much as 90% of topical eye drops is wasted or is not absorbed intraocularly (Chang 1988; Gupta 2012; Lee 1986). When drug absorption into the eye is limited, most of the medication is absorbed into the nasopharyngeal mucosa through the nasolacrimal duct. With increased contact time between topically applied medicine and the ocular surface, and with obstruction of drainage of the medicine into the nasopharyngeal mucosa, intraocular medicine concentrations may be increased. When more of the medicine remains available locally, a greater number of medicine molecules may reach the intended intraocular receptors, increasing the desired ocular effects, and fewer medicine molecules may reach the circulatory system, decreasing undesired adverse events through systemic absorption. Numerous reports have described cardiovascular and respiratory complications associated with timolol, a widely used nonselective beta-antagonist antiglaucoma medication, since its introduction in 1978 (Katz 1983; Levine 1982; Zimmerman 1981). Topical medication instillation techniques have been reported not only to reduce systemic timolol absorption (Kaila 1986; Passo 1984; Zimmerman 1984) but also to enhance ocular penetration of the medicine (Ellis 1992; Fraunfelder 1976; Zimmerman 1984).

Why it is important to do this review

Various topical medication instillation techniques have been recommended for administering ocular treatments. Some studies

suggest that NLO or ELC may enhance intraocular absorption (Ellis 1992; Fraunfelder 1976; Zimmerman 1984), reduce systemic absorption (Kaila 1986; Passo 1984; Zimmerman 1984), or both, of topically applied glaucoma medications. However, it is unclear whether reducing systemic absorption or enhancing intraocular absorption leads to an increased therapeutic effect of medication (Sleath 2011). Because of these controversies, it is necessary to review and summarize data regarding instillation techniques for their effectiveness, feasibility, and practicality systematically. However, to date no such review has been published (Li 2012).

OBJECTIVES

To investigate the effectiveness of topical medication instillation techniques compared with usual care or another method of instillation of topical medication in the management of glaucoma or ocular hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs).

Types of participants

We included RCTs of participants who had been prescribed topical eye medication for the treatment or control of glaucoma, including POAG, primary angle-closure glaucoma (PACG), and secondary glaucomas (such as pigmentary glaucoma or pseudoexfoliative glaucoma). We also included studies of participants with ocular hypertension or suspected to have glaucoma.

Types of interventions

We included RCTs that had compared topical medication instillation techniques with usual care or another method of instillation of topical medication. Topical medication instillation techniques may have included ELC, NLO, making sure the dropper does not touch the ocular area, instillation of drops into the conjunctival sac, removal of excess fluid after instillation, and delayed time interval between instillation of multiple topical medications.

Types of outcome measures

Primary outcomes

- Reduction of IOP from baseline measured as the:
  - proportion of participants with IOP less than 21 mmHg at one year;
  - mean IOP change from baseline at one year.

Secondary outcomes

- Participant-reported outcomes related to the ease, convenience, and comfort of instillation techniques
- Physiologic measurements of systemic absorption
- Escalation of therapy (such as added medications, laser trabeculoplasty, surgery, or a combination of these).
- Mean change in IOP
- Mean change in visual fields (mean deviation)
- Optic nerve progression (measured by mean change in cup/disk ratio)
- Mean change in best-corrected visual acuity
- Development of glaucoma among baseline glaucoma suspects or ocular hypertensive medications at three months, six months, one year, and subsequent years of follow-up.
- Quality of life outcomes.
- Cost-effectiveness outcomes.
- Adverse events.

Adverse events

We documented and compared ocular and systemic adverse events. Commonly reported ocular and systemic adverse events for various glaucoma drug classes are shown in Table 1.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for RCTs. There were no language or publication year restrictions. The date of the search was 8 December 2016.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12) (which contains the Cochrane Eyes and Vision Trials Register) (searched 8 December 2016) (Appendix 1);
- MEDLINE Ovid (1946 to 8 December 2016) (Appendix 2);
- Embase Ovid (1980 to 8 December 2016) (Appendix 3);
- PubMed (1948 to 8 December 2016) (Appendix 4);
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 8 December 2016) (Appendix 5);
- International Pharmaceutical Abstracts (1970 to 8 December 2016) (Appendix 6);
- *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com; last searched 13 May 2013) (Appendix 7);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 8 December 2016) (Appendix 8);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp; searched 8 December 2016) (Appendix 9).

Searching other resources

We searched the reference lists of included studies for additional studies not identified by the electronic searches. We used the Science Citation Index (Web of Science) to search for additional studies that may have cited included studies. We did not handsearch journals or conference abstracts specifically for the purpose of this review.

Data collection and analysis

Selection of studies

Two review authors independently assessed titles and abstracts identified through the searches and classified each record as relevant or potentially relevant, unclear, or definitely not relevant to this review. We obtained the full-text report for records classified as relevant or potentially relevant and unclear, two review authors independently assessed each reported study for inclusion or

exclusion. We documented excluded studies after review of the full-text report, with reasons for excluding (see Characteristics of excluded studies table). When a study's eligibility was unclear after full-text review, we planned to contact the authors of the publication for clarification; however, it was not necessary to contact any authors for this purpose. We resolved discrepancies at all stages of assessment by discussion.

Data extraction and management

Two review authors independently extracted data related to study characteristics, methodology, and outcomes using data forms developed by Cochrane Eyes and Vision for the purposes of this review. One review author entered the data into Review Manager 5 (RevMan 2014), and a second review author verified the data entered. We resolved discrepancies in data extraction and data entry by discussion. We attempted to contact study investigators to obtain desired information when not reported or unclearly reported. Whenever no response or clarification was received within six weeks, we used the data available or reported the study results as unclear.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study for potential sources of systematic bias according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered the following parameters when assessing risk of bias.

- Selection bias (random sequence generation and allocation concealment before randomization).
- Performance bias (masking of study personnel).
- Detection bias (masking of outcome assessors).
- Attrition bias (completeness of follow-up and intention-to-treat analysis).
- Reporting bias (selective outcome reporting).
- Other potential sources of bias (such as funding source when it could influence study methods or outcomes).

Masking of study participants was not assessed at the study level because of the paired-eye design of the included studies and the need to maintain the randomly assigned treatment of each eye.

We assessed each study for each risk of bias parameter as having a 'low risk of bias,' a 'high risk of bias,' or an 'unclear risk of bias' (insufficient information to permit judgment of low or high risk). We attempted to contact study investigators whenever the methods were unclear or when additional information was needed to make an assessment. Whenever no response or clarification was received within six weeks, we assessed the study on the basis of available information. We resolved disagreements between review authors through discussion.

Measures of treatment effect

We planned to report dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI). We considered the proportions of participants with IOP less than 21 mmHg, development of glaucoma among suspects or other at risk, escalation of therapy, and adverse events as dichotomous outcomes.

We planned to report continuous outcomes as mean differences (MD) between groups with 95% CIs. We considered mean IOP change, mean change in visual fields, optic nerve progression based on cup-to-disk ratio, mean change in best-corrected visual acuity, physiologic measures of systemic absorption, quality of life outcomes, and cost-effectiveness outcomes as continuous outcomes.

Participant-reported outcomes related to the ease, convenience, and comfort of instillation techniques may vary substantially; thus, we planned to assess these outcomes as reported by included studies.

Unit of analysis issues

The unit of analysis was the eye in both included studies as both had used a within-person, paired-eye design. Investigators of one trial used a mixed model with two levels of clustering (participant and eye level) to account for the within-person design (Maul 2012). The other study did not use a paired analysis to account for the correlation of characteristics and outcomes between the two eyes of a person and data were not reported in a manner that we could reanalyze outcomes in a paired analysis (Centofanti 2006). We reported the data as provided in the study reports.

Dealing with missing data

We planned to contact study investigators to ask for additional information when data were missing or incomplete. We set the response time at six weeks; when no reply was received in that time, we used the data available.

Assessment of heterogeneity

Clinical heterogeneity among studies was assessed on the basis of characteristics of participants, including glaucoma status and length of time with glaucoma, age, race, and underlying comorbidities (such as arthritis). We also assessed heterogeneity among instillation methods, such as which type of method was used, how many medications were used, and whether medications were self-administered or administered by a caregiver. We compared outcomes based on five elements (domain, specific measurement, specific metric, method of aggregation, and time points; Saldanha 2014) to determine whether meta-analysis was feasible. Due to lack of common outcomes reported in the trials, we were unable to combine data in meta-analyses. If meta-analysis is performed in future updates of the review, we will use the I^2 test to examine statistical heterogeneity. An I^2 value greater than 60% will be interpreted as indicating substantial statistical heterogeneity. If substantial statistical heterogeneity is present, we will not conduct a meta-analysis but instead will report the study results independently.

Assessment of reporting biases

We assessed selective outcome reporting bias at the individual study level. We compared outcomes that were specified a priori when study protocols or trial registry records were available, or outcomes that were measured as described in the methods section of a study report, with reported study results to classify studies as having high, low, or unclear risks of selective outcome reporting bias. We did not examine the symmetry of funnel plots to assess publication biases as described in the protocol for this review (Xu 2013), because we included only two studies in this review.

Data synthesis

If additional studies are included in future updates to this review, we will combine results in a meta-analysis when appropriate. We will use a fixed-effect model for meta-analyses that include fewer than three studies and a random-effects model for meta-analyses consisting of three or more studies. We will calculate summary MDs with 95% CIs for continuous outcomes and summary RRs with 95% CIs for dichotomous outcomes. For study results that are not adequate for meta-analysis, we will summarize the overall treatment effects for each outcome as reported by each study.

Subgroup analysis and investigation of heterogeneity

Because sufficient data were not available, we did not conduct planned subgroup analyses based on age (65 years and older), gender, race, type and number of medications, dose of medications, baseline glaucoma status (e.g., POAG, PACG, secondary glaucoma, glaucoma suspect, ocular hypertensive), and whether medications were instilled by the participant (self-administered) or by a caregiver.

Sensitivity analysis

We did not conduct planned sensitivity analyses to assess the impact of studies with high risk of bias, unpublished studies, and industry-funded studies because insufficient data were available. We also planned to conduct sensitivity analyses for studies in which the unit of analysis was the eyes rather than the participant.

'Summary of findings' table

We used the GRADE method to assess the certainty of evidence for each outcome reported in this review (GRADEpro 2014). Two review authors independently judged each outcome as very low-, low-, moderate-, or high-certainty according to the following five criteria: risk of bias, indirectness, heterogeneity, imprecision (wide CIs), and publication bias. We resolved any discrepancy by discussion. We produced a 'Summary of findings' table, which presents the comparative effects between treatments, to summarize the following main outcomes evaluated in this review: proportion of participants with IOP less than 21 mmHg; mean IOP change from baseline; participant-reported outcomes related to the ease, convenience, and comfort of instillation; physiologic measurements of systemic absorption, escalation of therapy, mean change in visual fields, and adverse events.

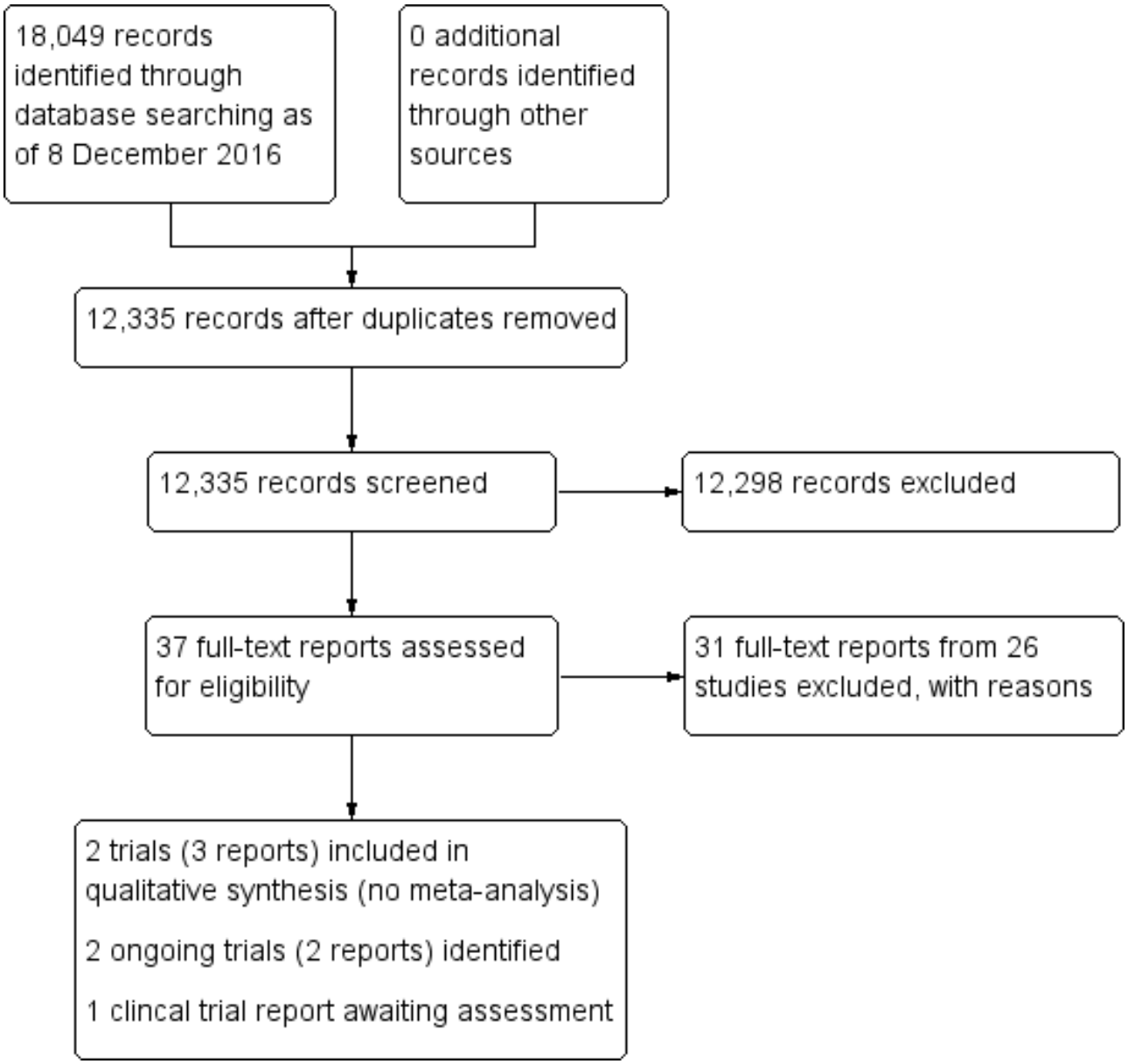
RESULTS

Description of studies

Results of the search

The electronic searches yielded 12,335 unique records after removing duplicates (Figure 1). We excluded 12,298 records by screening titles and abstracts, and 31 records (26 studies) after reviewing 37 full-text reports. We included two trials (three reports) in this review (Centofanti 2006; Maul 2012), identified two ongoing trials (NCT01416415; NCT02697318), and left one trial report as awaiting assessment until we can confirm whether the trial was initiated or completed (NCT01417689). We identified no additional eligible trials from searching other sources.

Figure 1. Study flow diagram.



Included studies

Types of participants

We included two within-person, RCTs (122 eyes of 61 participants); one trial was conducted in Italy (20 eyes of 10 participants) and one in the US (102 eyes of 51 participants). Both trials included men and women with bilateral glaucoma or ocular hypertension. One trial included only participants currently using prostaglandin monotherapy (latanoprost, travoprost, or bimatoprost) to reduce IOP (Maul 2012), while the other trial excluded past or current use of topical prostaglandins or prostamides (Centofanti 2006).

Types of interventions

Participants in both trials received prostaglandin monotherapy during the study; bimatoprost only in Centofanti 2006 and latanoprost, travoprost, or bimatoprost in Maul 2012. However, the instillation technique under investigation differed between the two trials. In Centofanti 2006, each participant wiped one eye with an absorbent pad after self-administration of drops to minimize absorption of the eye drops into the skin but did not wipe the contralateral eye after instillation. In Maul 2012, participants were randomized to keep one eye closed for either one or three minutes after self-administration of drops to increase the ocular effect of the eye drops. The fellow eyes of participants served as controls in both trials.

Types of outcomes

The outcomes assessed by each of the trials reflected the trial authors research question posed by the trial investigators and the type of instillation technique under investigation. The authors of Centofanti 2006 aimed to evaluate the dermatologic effects of removing excess fluid during and after instillation of bimatoprost

drops. Therefore, the outcomes assessed in the trial did not include IOP or vision-related measures and focused only on known dermatologic effects of prostaglandins (eyelash length, eyelash growth, skin hypertrichosis, and skin hyperpigmentation). Follow-up examinations to assess outcomes from this trial were at one, three, and four months.

The authors of Maul 2012 were interested in the effect of ELC on lowering IOP in chronic users of prostaglandin eye drops. IOP was the only outcome assessed in this trial and was measured one hour, one day, and final follow-up (7 to 14 days). Subgroup analysis was reported for participants randomized to one or three minutes of POAG (i.e. one minute versus fellow eye and three minutes versus fellow eye).

Neither trial reported the proportion of participants with IOP less than 21 mmHg; participant-reported outcomes related to the ease, convenience, and comfort of instillation techniques; physiologic measurements of systemic absorption; escalation of therapy (such as added medications, laser trabeculoplasty, surgery, or a combination of these); mean change in visual fields; optic nerve progression (measured by mean change in cup/disk ratio); mean change in best-corrected visual acuity; development of glaucoma among baseline glaucoma suspects; quality of life outcomes; or cost-effectiveness outcomes. No data from either trial were reported at follow-up times of more than four months.

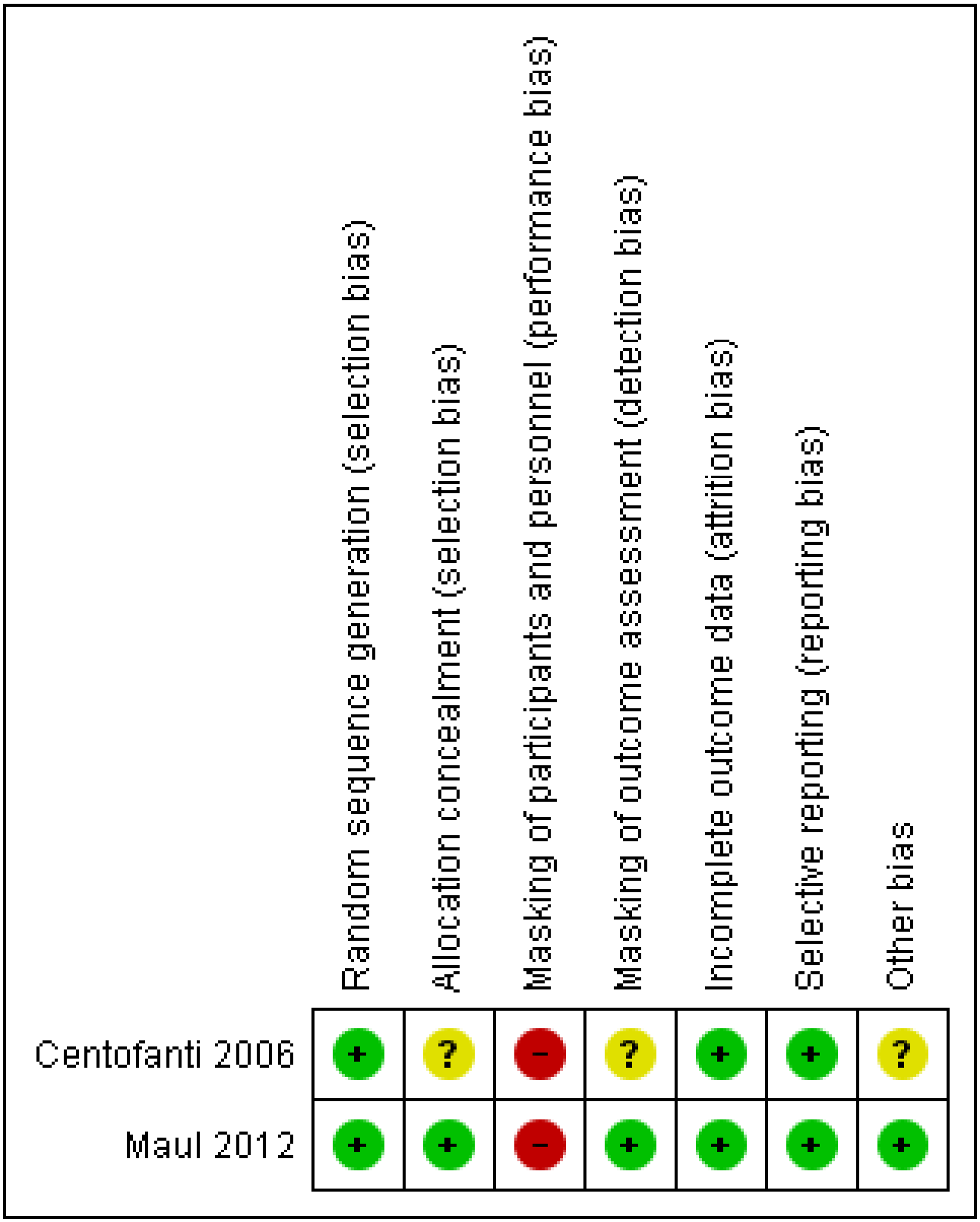
Excluded studies

We excluded 26 studies after review of the full-text reports. Reasons for excluding each study are presented in the Characteristics of excluded studies table. In summary, 11 studies did not use a randomized design, 20 studies did not evaluate interventions under the scope of this review, and two studies did not include participants with glaucoma. We excluded seven studies for more than one reason.

Risk of bias in included studies

We provide details of the 'Risk of bias' assessment for each trial in the Characteristics of included studies table and a summary in Figure 2.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

We assessed Maul 2012 at low risk of selection bias because the randomization was computer generated and allocation of treatment assignments were concealed by use of sequentially numbered, opaque, sealed envelopes that were opened only at the time of randomization. Centofanti 2006 used computer-generated

randomization; however, no methods were reported in regards to allocation concealment before randomization.

Masking (performance bias and detection bias)

We assessed both trials at high risk of performance bias because masking of participants was not feasible with the interventions under investigation and there was the possibility of a cross-over (contamination) effect between groups due to the paired-eye design of the studies (i.e. participants may have applied eye drops to both eyes in the same manner). We assessed Maul 2012 at low risk of detection bias because outcome assessors were masked to treatment assignment and Centofanti 2006 at unclear risk because it was not reported whether study personnel who collected and measured eyelashes were masked. However, assessors or skin-related outcomes were masked in Centofanti 2006.

Incomplete outcome data

In both trials, all participants completed the study and eyes were analyzed as randomized. Therefore, we assessed both trials had low or no risk of attrition bias.

Selective reporting

We assessed both trials at low risk of reporting bias. Although there were minor differences between the trial registry record and journal publication for Maul 2012, both reports indicated that change in IOP was the primary and only outcome of interest. There was no protocol or trial registry record found for Centofanti 2006; however, all outcome measures that were described in the methods section of the study publication were reported in the results section.

Other potential sources of bias

We identified no other potential sources of bias for Maul 2012. The authors of Centofanti 2006 did not report sources of funding or declare no financial interests; therefore, we assessed this trial at unclear risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Topical medication instillation techniques for glaucoma

We performed no meta-analyses for this review as the included trials did not evaluate the same instillation techniques or report the same outcomes. Maul 2012 reported only mean change in IOP, which compared POAG versus no POAG after instilling prostaglandin drops in 102 eyes of 51 participants. Centofanti 2006 reported only outcomes related to dermatologic adverse events among 20 eyes of 10 participants to test the utility of removing excess fluid during and after instillation of bimatoprost drops.

There were no data available for the other outcomes that we specified in the protocol for this review. Neither trial reported outcomes at one year, the primary follow-up time specified in our protocol from the review.

Mean change in intraocular pressure

One trial reported outcomes for mean change in IOP from baseline (Maul 2012). At one to two weeks' follow-up, the MD in IOP change was -0.33 mmHg (95% CI -0.8 to 1.5; 51 participants) when comparing the ELC group with the no ELC group (estimated using a mixed model to account for the within-person design). Results of the MD in IOP change from baseline were similar when analyzing by subgroups of ELC for one minute (0.41 mmHg, 95% CI -1.0 to 1.9; 25 participants) and three minutes (0.86 mmHg, 95% CI -0.6 to 2.3; 26 participants). We did not consider the mean difference in IOP change between to be clinically meaningful. We graded the certainty of evidence as moderate, downgrading one level for risk of performance bias.

Adverse events

One trial reported outcomes related to adverse events (Centofanti 2006). At four months' follow-up, eyelashes were shorter among eyes that participants had wiped to remove excess fluid compared with fellow eyes that were not wiped (MD -1.70 mm, 95% CI -3.46 to 0.06; 10 participants). Furthermore, 5 of 10 eyes in the fluid removal group compared with 9 of 10 eyes in the no removal group experienced eyelash growth of more than 1.5 mm (RR 0.11, 95% CI 0.01 to 1.24). We graded the certainty of evidence as low, downgrading one level for risk of performance and detection bias and one level for imprecision.

Centofanti 2006 also reported adverse events on the skin around the eyes at four months' follow-up. Fewer eyes showed skin hyperpigmentation in the eyelid region towards the nose in the fluid removal group (1 of 10) compared with the no removal group (6 of 10) (RR 0.07, 95% CI 0.01 to 0.84). However, the difference was not as prominent in the eyelid region towards the temples (4 of 10 eyes in the fluid removal group and 6 of 10 eyes in the no removal group; RR 0.44, 95% CI 0.07 to 2.66). The proportion with hypertrichosis (excessive hair growth) was 6 of 10 eyes in both groups (RR 1.00, 95% CI 0.17 to 5.98). We graded the certainty of evidence as low, downgrading one level for risk of performance bias and one level for imprecision.

DISCUSSION

Summary of main results

Our comprehensive search for RCTs investigating the effectiveness of proposed topical medication instillation techniques in the management of glaucoma included only two studies (Centofanti 2006; Maul 2012). The two studies randomly selected one eye of 61 participants who received bilateral prostaglandin monotherapy to instill a topical medication using a potentially beneficial technique to reduce adverse events or increase IOP-lowering effects, and the fellow eye acted as the within-person control.

One study evaluated the effect of removing excess fluid to minimize dermatologic adverse events of bimatoprost 0.03% topical therapy. In Centofanti 2006, there was a smaller proportion of regional dermatologic skin changes in the eyes when removing excess fluid compared with not removing excess fluid. However, reducing the drop-skin contact during drop instillation minimized the incidence of regional dermatologic adverse events, but not for the entire periocular area.

One study investigates the effect of ELC to enhance the IOP-lowering effect after self-administration of prostaglandin drops on lowering IOP. In Maul 2012, there was no additional IOP reduction in the ELC group.

Overall completeness and applicability of evidence

The two studies included in our review evaluated two topical medication instillation techniques for prostaglandin analog monotherapy (Centofanti 2006; Maul 2012), which is the most frequently prescribed initial agent for lowering IOP (Garway-Heath 2015; McKinnon 2008). Dermatologic adverse events from topical prostaglandins are well documented and may not apply to other types of IOP-lowering drug classes. It also is unknown whether the effect of topical medication instillation techniques differs among different drug classes.

We found no evidence for other topical medication instillation techniques (e.g. NLO). For beta-blockers, such as timolol, commonly associated adverse events are cardiovascular and respiratory complications. Thus, preventive measures may be aimed to reduce systemic absorption, therefore, evaluation of NLO would be of more interest than other instillation techniques for many IOP-lowering agents. The effectiveness of punctal plugs (plugs inserted into the tear duct to block the medications from draining from the eye and to reduce systemic absorption), which were not included in the scope of this review, also would be of interest.

Centofanti 2006 and Maul 2012 were conducted in Italy and the US, respectively. These regions have well-developed healthcare systems; thus, it is unknown how the estimates from these studies may apply to cases of glaucoma in countries with less developed and lower income health systems. For example, relatively cheaper agents, such as beta-blockers, are the most commonly used antiglaucoma agents in some countries. Also, POAG is the most common glaucoma type in the US; participants in Maul 2012 were predominantly white people with the baseline IOP of 18 mmHg. It is unknown how outcome estimates from this study may apply to cases of glaucoma in Asian countries where, for example, PACG is more common and has higher baseline IOP levels. Absolute level of changes in IOP differ by baseline levels in that eyes with higher IOP levels at baseline have more potential to be reduced than eyes with lower IOP levels at baseline.

Quality of the evidence

One study included in this review was well designed, reported clearly, and had low risk of bias overall except it had high performance bias; thus, we assessed the certainty of evidence from this review as moderate (Maul 2012). However, it is important to note that follow-up was brief at only one to two weeks, which may be too short to observe therapeutic differences between groups and allow for cyclical fluctuations in IOP.

One study provided low-certainty evidence for dermatologic adverse events (downgraded for performance bias, detection bias, imprecision, or a combination of these). Although estimates were imprecise, Centofanti 2006 showed that reducing the drop-skin contact may minimize the incidence of regional dermatologic adverse events and eyelash growth.

Potential biases in the review process

We used standard Cochrane methodological procedures to minimize potential biases in the review process. We reported all outcomes that were specified in the protocol for this review or reported that no data were available for specified outcomes.

Agreements and disagreements with other studies or reviews

Although non-randomized studies suggest that NLO or ELC may be used to reduce systemic absorption (Flach 2008; Kaila 1986; Passo 1984; Zimmerman 1984) and enhance ocular penetration (Ellis 1992; Flach 2008; Fraunfelder 1976; Zimmerman 1984) of the topical agents, the evidence of effects on IOP control is inconclusive. As one type of topical instillation techniques, ELC is thought to increase the contact time between the ocular area and drops, which in turn, aims to improve ocular bioavailability. However, the additional bioavailability by enhanced ocular penetration of the medicine by ELC has not been shown to bring about increased IOP-lowing effects that can be detected clinically.

This review included one RCT which directly measured the IOP-lowering of ELC in chronic users of prostaglandin eye drops for the treatment of glaucoma. The lack of significant differences between the intervention group and the control group concurs with reports by other non-randomized studies and clinical observations with NLO (Huang 1989; Sharir 1994).

The latest American Academy of Ophthalmology's Preferred Practice Pattern on Primary Open Angle Glaucoma (AAO 2015) recommends educating people using eye drops to lower IOP about ELC and NLO techniques to reduce systemic absorption; however, there was no evidence cited that either supported or refuted that ELC alone, NLO alone, or both are effective means to lower IOP.

AUTHORS' CONCLUSIONS

Implications for practice

This review identified a paucity of evidence to inform robust conclusions for topical instillation techniques treating glaucoma in practice.

One study of participants receiving chronic bilateral prostaglandin monotherapy randomized one eye to eyelid closure (ELC), while the fellow eye served as within-person control, provided moderate-certainty evidence of a minimal difference between the ELC group and the no ELC group with respect to intraocular pressure (IOP) change from baseline. In another study, participants were instructed to wipe one eye with an absorbent pad after administration of prostaglandin eye drops. The fellow eye acted as the within-person control and was not wiped. There was a reduction of the incidence and extent of dermatologic adverse events in the nasal region; however, this difference was not observed in the temporal region. The results from these small studies should be interpreted cautiously as these data represent only two types of instillation techniques and these results are not necessarily applicable to other antiglaucoma topical agents.

Implications for research

There is a need for well-designed and adequately powered parallel-group RCTs to determine:

- whether topical instillation techniques aimed at increasing ocular absorption of drops can enhance the IOP-lowering effect of most antiglaucoma agents;
- which topical instillation technique is favorable over others to enhance IOP-lowering effects;

- whether the topical instillation techniques aimed at reducing systemic absorption of drops or obstructing the medicine into the nasopharyngeal mucosa can minimize local or systemic adverse events.

In order to enroll a sufficiently large and diverse sample size, future randomized controlled trials should be multi-centered with a central coordinating center to ensure adherence to methodologic standards and consistency of protocols is maintained across all study sites. Although masking of participants and some study personnel are not feasible, using a parallel-group rather than paired-eye design could minimize potential cross-over effects and performance bias. Outcome assessors should remain masked to treatment assignments until the trial ends and data have been analyzed. In addition to IOP change as a primary outcome of interest, other clinical and participant-centered outcomes should be assessed, such as changes in visual field parameters, best-corrected visual acuity, participant-reported outcomes related to the ease, convenience and comfort of instillation techniques, and adverse events.

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REFERENCES

References to studies included in this review

Centofanti 2006 *{published data only}*

Centofanti M, Oddone F, Chimenti S, Tanga L, Citarella L, Manni G. Prevention of dermatologic side effects of bimatoprost 0.03% topical therapy. *American Journal of Ophthalmology* 2006;**142**(6):1059-60.

Maul 2012 *{published data only}*

Maul EA, Friedman DS, Quigley HA, Jampel HD. Impact of eyelid closure on the intraocular pressure lowering effect of prostaglandins: a randomised controlled trial. *British Journal of Ophthalmology* 2012;**96**(2):250-3.

References to studies excluded from this review

Ariturk 1996 *{published data only}*

Ariturk N, Oge I, Erkan D, Sullu Y, Sahin M. The effects of nasolacrimal canal blockage on topical medications for glaucoma. *Acta Ophthalmologica* 1996;**74**(4):411-3.

Bartlett 1996 *{published data only}*

Bartlett JD, Boan K, Corliss D, Gaddie IB, Punctal Plugs in Glaucoma Study Group. Efficacy of silicone punctal plugs as adjuncts to topical pharmacotherapy of glaucoma - a pilot study. *Journal of the American Optometric Association* 1996;**67**(11):664-8.

Beckers 2013 *{published data only}*

Beckers HJ, Webers CA, Busch MJ, Brink HM, Colen TP, Schouten JS, et al. Adherence improvement in Dutch glaucoma patients: a randomized controlled trial. *Acta Ophthalmologica* 2013;**91**(7):610-8.

Bohm 2014 *{published data only}*

Bohm MR, Lill TM, Eter N, Prokosch-Willing V. Alterations of intraocular pressure in comparison of self- and external-administered topical antiglaucomatosa during diurnal intraocular pressure measurements. *Klinische Monatsblatter Fur Augenheilkunde* 2014;**231**(8):810-7.

Brinchmann-Hansen 1979 *{published data only}*

Brinchmann-Hansen O, Anmarkrud N. Pilocarpine medication in open-angle glaucoma. A study using pilocarpine eyedrops and an ocular therapeutic system. *Acta Ophthalmologica* 1979;**57**(1):55-62.

Brown 1984 *{published data only}*

Brown MM, Brown GC, Spaeth GL. Improper topical self-administration of ocular medication among patients with glaucoma. *Canadian Journal of Ophthalmology* 1984;**19**(1):2-5.

De Smet 2000 *{published data only}*

De Smet PA, Van Drooge MJ. How glaucoma patients use their eye drops: potential effects of administration difficulties. *Pharmaceutisch Weekblad* 2000;**135**:1096-9.

Doe 1997 *{published data only}*

Doe EA, Campagna JA, Dirhs MS, Johnson AJ. Timolol 0.5% spray vs. timolol 0.5% drops for the control of intraocular pressure. *American Academy of Ophthalmology* 1997:196.

Flach 2008 *{published data only}*

Flach AJ. The importance of eyelid closure and nasolacrimal occlusion following the ocular instillation of topical glaucoma medications, and the need for the universal inclusion of one of these techniques in all patient treatments and clinical studies. *Transactions of the American Ophthalmological Society* 2008;**106**:138-45.

Halberg 1975 *{published data only}*

Halberg GP, Kelly SE, Morrone M. Drug delivery systems for topical ophthalmic medication. *Annals of Ophthalmology* 1975;**7**(9):1199-204.

Harris 1975 *{published data only}*

Harris LS, Kahanowicz Y. Pump infusion of pilocarpine. *Ophthalmologica* 1975;**171**(2):157-64.

Huang 1989 *{published data only}*

Huang TC, Lee DA. Punctal occlusion and topical medications for glaucoma. *American Journal of Ophthalmology* 1989;**107**(2):151-5.

Moolasarn 2007 *{published data only}*

Moolasarn S, Srisanga S. The effects of health education program using the health belief model on changing self care behaviors and treatment outcomes of primary glaucoma patients. *Thai Journal of Hospital Pharmacy* 2007;**17**(2):128-38.

Nordmann 2009 *{published data only}*

Nordmann JP, Baudouin C, Bron A, Denis P, Rouland JF, Sellem E, et al. Xal-Ease: impact of an ocular hypotensive delivery device on ease of eyedrop administration, patient compliance, and satisfaction. *European Journal of Ophthalmology* 2009;**19**(6):949-56.

Okeke 2009 *{published data only}*

Okeke CO, Quigley HA, Jampel HD, Ying GS, Plyler RJ, Jiang Y, et al. Interventions improve poor adherence with once daily glaucoma medications in electronically monitored patients. *Ophthalmology* 2009;**116**(12):2286-93.

Opitz 2011 *{published data only}*

Opitz D, Tung S, Park J, Jang U. Silicone punctal plugs as an adjunctive therapy to travoprost 0.004% ophthalmic solution in primary open angle glaucoma and ocular hypertension. American Academy of Optometry Annual Meeting; 2009 November 11-14: Orlando (FL). Orlando (FL): American Academy of Optometry, 2009.

* Opitz DL, Tung S, Jang US, Park JJ. Silicone punctal plugs as an adjunctive therapy for open-angle glaucoma and ocular hypertension. *Clinical and Experimental Optometry* 2011;**94**(5):438-42.

Passo 1984 *{published data only}*

Passo MS, Palmer EA, Van Buskirk EM. Plasma timolol in glaucoma patients. *Ophthalmology* 1984;**91**(11):1361-3.

Rotberg 2006 *{published data only}*

Rotberg M, Bosworth C, Pleil AM, Zhang M, Paggiarino D. Comparison of eyedrop delivery using either a novel horizontal delivery device or a conventional dropper bottle. Investigative Ophthalmology and Visual Science 2006; Vol. 47:ARVO E-abstract 456.

Sakiyalak 2014 *{published data only}*

Sakiyalak D, Maneephagaphun K, Metheetrairat A, Ruangvaravate N, Kitnarong N. The effect of the Thai "Eye Drop Guide" on success rate of eye drop self-instillation by glaucoma patients. *Asian Biomedicine* 2014;**8**(2):221-7.

Sharir 1994 *{published data only}*

Sharir M, Zimmerman TJ. Effect of nasolacrimal occlusion on dose and duration of action of tropical ocular hypotensive agents. *Advances in Therapy* 1993;**10**(2):74-85.

* Sharir M, Zimmerman TJ. Nasolacrimal occlusion improves the therapeutic index of antiglaucoma medications. *Journal of the Association for Academic Minority Physicians* 1994;**5**(2):62-7.

Zimmerman TJ, Sharir M, Nardin GF, Fuqua M. Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion. *American Journal of Ophthalmology* 1992;**114**(1):8-13.

Zimmerman TJ, Sharir M, Nardin GF, Fuqua M. Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion. *American Journal of Ophthalmology* 1992;**114**(1):1-7.

Sharma 2016 *{published data only}*

Sharma R, Singhal D, Shashni A, Agarwal E, Wadhwani M, Dada T. Comparison of eye drop instillation before and after use of drop application strips in glaucoma patients on chronic topical therapy. *Journal of Glaucoma* 2016;**25**(4):e438-40.

Shedden 2001 *{published data only}*

Shedden A, Laurence J, Tipping R. Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution versus timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study. *Clinical Therapeutics* 2001;**23**(3):440-50.

Simel 1988 *{published data only}*

Simel DL, Simel PJ. Does lacrimal duct occlusion decrease intraocular pressure in patients refractory to medical treatment for glaucoma? A randomized, sham-controlled, crossover trial. *Journal of Clinical Epidemiology* 1988;**41**(9):859-65.

Stewart 2002 *{published data only}*

Stewart WC, Sharpe ED, Stewart JA, Hott CE. The safety and efficacy of timolol 0.5% in xanthan gum versus timolol gel forming solution 0.5%. *Current Eye Research* 2002;**24**(5):387-91.

Urtti 1994 *{published data only}*

Urtti A, Rouhiainen H, Kaila T, Saano V. Controlled ocular timolol delivery: systemic absorption and intraocular pressure effects in humans. *Pharmaceutical Research* 1994;**11**(9):1278-82.

Zimmerman 1984 *{published data only}*

Zimmerman TJ, Kooner KS, Kandarakis AS, Ziegler LP. Improving the therapeutic index of topically applied ocular drugs. *Archives of Ophthalmology* 1984;**102**(4):551-3.

References to studies awaiting assessment

NCT01417689 *{published data only}*

NCT01417689. Eyedrop instillation technique: a randomized controlled trial. clinicaltrials.gov/ct2/show/NCT01417689 Date first received: 15 August 2011.

References to ongoing studies

NCT01416415 *{published data only}*

NCT01416415. Glaucoma eye drop instillation: impact of education. clinicaltrials.gov/ct2/show/NCT01416415 Date first received: 11 August 2011.

NCT02697318 *{published data only}*

NCT02697318. Evaluation of a new method for instilling eye drops. clinicaltrials.gov/ct2/show/NCT02697318 Date first received: 29 February 2016.

Additional references

AAO 2015

American Academy of Ophthalmology (AAO) Preferred Practice Pattern Glaucoma Panel. Primary Open-Angle Glaucoma PPP - 2015. www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp-2015 (accessed 8 February 2017).

Alsbirk 1976

Alsbirk PH. Primary angle-closure glaucoma: oculometry, epidemiology, and genetics in a high risk population. *Acta Ophthalmologica Supplementum* 1976;**127**:5-31.

Armaly 1980

Armaly MF, Krueger DE, Maunder L, Becker B, Hetherington J Jr, Kolker AE, et al. Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Archives of Ophthalmology* 1980;**98**(12):2163-71.

Beckers 2008

Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2008;**246**(10):1485-90.

Bourlais 1998

Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems - recent advances. *Progress in Retinal and Eye Research* 1998;**17**(1):33-58.

Cantor 1989

Cantor LB. Systemic side effects of glaucoma medications. *Indiana Medicine* 1989;**82**(2):105-7.

Casson 2012

Casson RJ, Chidlow G, Wood JP, Crowston JG, Goldberg I. Definition of glaucoma: clinical and experimental concepts. *Clinical and Experimental Ophthalmology* 2012;**40**(4):341-9.

Chang 1988

Chang SC, Chien DS, Bundgaard H, Lee VH. Relative effectiveness of prodrug and viscous solution approaches in maximizing the ratio of ocular to systemic absorption of topically applied timolol. *Experimental Eye Research* 1988;**46**(1):59-69.

Coleman 2008

Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Survey of Ophthalmology* 2008;**53**(6):S3-10.

Congdon 2004

Congdon N, O'Colmain B, Klaver CC, Klein R, Muñoz B, Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Archives of Ophthalmology* 2004;**122**(4):477-85.

Ehongo 2007

Ehongo A, Bremer F. Ocular side effects of glaucoma treatment agents. *Bulletin de la Societe Belge d Ophtalmologie* 2007;**304**:103-10.

Ellis 1992

Ellis PP, Wu PY, Pfoff DS, Bloedow DC, Riegel MR. Effect of nasolacrimal occlusion on timolol concentrations in the aqueous humor of the human eye. *Journal of Pharmaceutical Sciences* 1992;**81**(3):219-20.

Ernest 2013

Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual field progression. *Ophthalmology* 2013;**120**(3):512-9.

Fraunfelder 1976

Fraunfelder FT. Extraocular fluid dynamics: how best to apply topical ocular medication. *Transactions of the American Ophthalmological Society* 1976;**74**:457-87.

Garway-Heath 2015

Garway-Heath DF, Crabb DP, Bunce C, Lascaratos G, Amalfitano F, Anand N, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015;**385**(9975):1295-304.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

GRADEpro 2014 [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 15 January 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Gupta 2012

Gupta R, Patil B, Shah BM, Bali SJ, Mishra SK, Dada T. Evaluating eye drop instillation technique in glaucoma patients. *Journal of Glaucoma* 2012;**21**(3):189-92.

Heijl 2009

Heijl A, Bengtsson B, Hyman L, Leske MC, Early Manifest Glaucoma Trial Group. Natural history of open-angle glaucoma. *Ophthalmology* 2009;**116**(12):2271-6.

Higgins 2011

Higgins JP, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Ismail 2016

Ismail R, Azuara-Blanco A, Ramsay CR. Consensus on outcome measures for glaucoma effectiveness trials: results from a Delphi and nominal group technique approaches. Journal of Glaucoma 2016; Vol. 25, issue 6:539-46.

Kaila 1986

Kaila T, Huupponen R, Salminen L. Effects of eyelid closure and nasolacrimal duct occlusion on the systemic absorption of ocular timolol in human subjects. *Journal of Ocular Pharmacology* 1986;**2**(4):365-9.

Katz 1983

Katz IM. Side effects of topical ocular timolol. *American Journal of Ophthalmology* 1983;**96**(4):552-3.

Landers 2002

Landers J, Goldberg I, Graham SL. Analysis of risk factors that may be associated with progression from ocular hypertension to primary open angle glaucoma. *Clinical and Experimental Ophthalmology* 2002;**30**(4):242-7.

Le 2003

Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. *Investigative Ophthalmology and Visual Science* 2003;**44**(9):3783-9.

Lee 1986

Lee VH, Robinson JR. Topical ocular drug delivery: recent developments and future challenges. *Journal of Ocular Pharmacology* 1986;**2**(1):67-108.

Lee 2005

Lee DA, Higginbotham EJ. Glaucoma and its treatment: a review. *American Journal of Health-System Pharmacy* 2005;**62**(7):691-9.

Levine 1982

Levine L. Clinical implications of reported timolol-induced side effects. *American Journal of Optometry and Physiological Optics* 1982;**59**(6):523-8.

Li 2012

Li T, Vedula SS, Scherer R, Dickersin K. What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. *Annals of Internal Medicine* 2012;**156**(5):367-77.

Marquis 2005

Marquis RE, Whitson JT. Management of glaucoma: focus on pharmacological therapy. *Drugs and Aging* 2005;**22**(1):1-21.

McKinnon 2008

McKinnon SJ, Goldberg LD, Peeples P, Walt JG, Bramley TJ. Current management of glaucoma and the need for complete therapy. *American Journal of Managed Care* 2008;**14**(1 Suppl):S20-7.

Medeiros 2003

Medeiros FA, Sample PA, Zangwill LM, Bowd C, Aihara M, Weinreb RN. Corneal thickness as a risk factor for visual field loss in patients with preperimetric glaucomatous optic neuropathy. *American Journal of Ophthalmology* 2003;**136**(5):805-13.

Noecker 2006

Noecker RJ. The management of glaucoma and intraocular hypertension: current approaches and recent advances. *Therapeutics and Clinical Risk Management* 2006;**2**(2):193-206.

Pan 2011

Pan Y, Varma R. Natural history of glaucoma. *Indian Journal of Ophthalmology* 2011;**59**(Suppl):S19-23.

Quigley 1996

Quigley HA. Number of people with glaucoma worldwide. *British Journal of Ophthalmology* 1996;**80**(5):389-93.

Quigley 2006

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology* 2006;**90**(3):262-7.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Saldanha 2014

Saldanha IJ, Dickersin K, Wang X, Li T. Outcomes in Cochrane systematic reviews addressing four common eye conditions: an evaluation of completeness and comparability. *PLoS One* 2014;**9**(10):e109400.

Shell 1984

Shell JW. Ophthalmic drug delivery systems. *Survey of Ophthalmology* 1984;**29**(2):117-28.

Sleath 2011

Sleath B, Blalock S, Covert D, Stone JL, Skinner AC, Muir K, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. *Ophthalmology* 2011;**118**(12):2398-402.

Smith 2012

Smith S, Fagien S, Whitcup SM, Ledon F, Somogyi C, Weng E, et al. Eyelash growth in subjects treated with bimatoprost: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. *Journal of the American Academy of Dermatology* 2012;**66**(5):801-6.

Tham 2014

Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;**121**(11):2081-90.

Tielsch 1996

Tielsch JM. The epidemiology and control of open angle glaucoma: a population-based perspective. *Annual Review of Public Health* 1996;**17**:121-36.

Zimmerman 1981

Zimmerman TJ, Leader BJ, Golob DS. Potential side effects of timolol therapy in the treatment of glaucoma. *Annals of Ophthalmology* 1981;**13**(6):683-9.

Zimmerman 1983

Zimmerman TJ, Zalta AH. Facilitating patient compliance in glaucoma therapy. *Survey of Ophthalmology* 1983;**28**(Suppl):252-8.

References to other published versions of this review

Xu 2013

Xu L, Wang X, Wu M. Topical medication instillation techniques for glaucoma. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: 10.1002/14651858.CD010520]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Centofanti 2006

Methods	**Study design:** within-person, randomized controlled trial **Number randomized:**

Centofanti 2006 *(Continued)*

	Total: 20 eyes of 10 participants Per group: 10 eyes of 10 participants **Exclusions or losses to follow-up after randomization:** none **Unit of analysis:** eyes **Number analyzed:** Total: 20 eyes of 10 participants Per group: 10 eyes of 10 participants **Power calculation:** not reported
Participants	**Country:** Italy **Mean age:** 56 years (range 31 to 79) **Gender:** 7 women (70%), 3 men (30%) **Inclusion criteria:** bilateral glaucoma or ocular hypertension **Exclusion criteria:** "past or current use of topical prostaglandins or prostamides, the need for more than one drug to control IOP, concomitant active ocular or dermatologic diseases, the use of sunless tanning products, or tanning booths in the past six months"
Interventions	**Intervention:** removal of excess fluid during and after instillation with an absorbent pad (TNT 7.5 × 7.5 cm, 4 layers; Ploing SRL Merchandising, Pomezia, Rome, Italy) **Control:** no removal of excess fluid with an absorbent pad **Glaucoma treatment:** bimatoprost 0.03% instilled in both eyes once a night for 4 months **Length of follow-up:** Planned: 4 months Actual: 4 months
Outcomes	**Outcomes, as specified in study report:** Eyelash length, in mm, measured by microscope using the longest eyelash from the upper eyelid Eyelash growth, the proportion with change > 1.5 mm from baseline Skin hypertrichosis, measured by digital contact dermatoscopy Skin hyperpigmentation, measured by digital contact dermatoscopy **Adverse events from intervention:** not reported **Intervals at which outcomes assessed:** 1, 3, and 4 months
Notes	**Trial registration:** not reported **Funding sources:** not reported **Disclosures of interest:** not reported **Study period:** not reported **Subgroup analyses:** none reported

Centofanti 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An electronic web-based randomization plan generator was used for randomization."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Masking of participants and personnel (performance bias)	High risk	Masking of participants not feasible with these interventions. Possibility of a cross-over effect between groups.
Masking of outcome assessment (detection bias)	Unclear risk	"Skin hypertrichosis and pigmentation were assessed by three investigators (who were blinded to the data) by means of digital contact dermatoscopy." Masking of people selecting and collecting the eyelashes and people measuring eyelash length not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study and were analyzed as randomized.
Selective reporting (reporting bias)	Low risk	No protocol or trial registry record available; however, all outcome measures reported in the methods of the study were reported in the results.
Other bias	Unclear risk	Sources of funding and financial interests not reported.

Maul 2012

Methods	**Study design:** within-person, randomized controlled trial **Number randomized:** Total: 102 eyes of 51 participants Per group: 25 eyes of 25 participants in the 1-minute group and 26 eyes of 26 participants in the 3-minute group; fellow eyes served as within-person control **Exclusions or losses to follow-up after randomization:** none **Unit of analysis:** eyes **Number analyzed:** Total: 102 eyes of 51 participants Per group: 25 eyes of 25 participants in the 1-minute group and 26 eyes of 26 participants in the 3-minute group; fellow eyes served as within-person control **Power calculation:** power of 90% with a significance of 5% to detect difference of 1.5 mmHg in the intervention compared with control eyes for 43 pairs of eyes
Participants	**Country:** US **Mean age:** 67 years (range not reported) **Gender:** 27 women (53%), 24 men (47%)

Maul 2012 *(Continued)*

	Inclusion criteria: chronic bilateral use of prostaglandin monotherapy (latanoprost, travoprost, or bimatoprost) to reduce IOP **Exclusion criteria:** ≤ 18 years, use of other IOP-lowering medications within 1 month of study, an abnormal slit lamp exam, previous incisional eye surgery, iridotomy, trabeculoplasty, or punctal occlusion
Interventions	**Intervention 1:** ELC for 1 minute after instillation **Intervention 2:** ELC for 3 minutes after instillation **Control:** no timed ELC after instillation **Glaucoma treatment:** same prostaglandin agent and regimen that participants were using prior to study enrollment, beginning 24 hours after first instillation; participants instilled drops in the intervention eye first, performed ELC as randomized, then instilled drops into the control eye **Length of follow-up:** Planned: 7 to 14 days Actual: 7 to 14 days
Outcomes	**Primary outcome, as specified in study report:** "IOP change from baseline in the intervention eye compared with the control eye" **Secondary outcome, as specified in study report:** "subgroup analysis for the effect of 1 min and 3 min ELC" **Adverse events from intervention:** not reported **Intervals at which outcomes assessed:** 1 hour, 1 day, and 7 to 14 days (final visit)
Notes	**Trial registration:** NCT00832832 **Funding sources:** National Institutes of Health, US **Disclosures of interest:** "None to declare" **Study period:** March 2009 to January 2010 **Subgroup analyses:** 1-minute and 3-minute ELC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were assigned by computerised random number to one of four groups: ELC for 1 or 3 min and intervention eye right or left."
Allocation concealment (selection bias)	Low risk	"The allocation sequence was concealed in sequentially numbered, opaque and sealed envelopes from the researchers (DSF, EAM, HDJ, HAQ) enrolling and assessing participants. The envelopes were opened only after the enrolled participants completed all baseline assessments including IOP measurement. The fellow eye not randomised to intervention served as a control."
Masking of participants and personnel (performance bias)	High risk	Masking of participants not feasible with these interventions. Possibility of a cross-over effect between groups.
Masking of outcome assessment (detection bias)	Low risk	"All IOP measurements in the study were obtained by a masked operator and a recorder who read the results independently."

Maul 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study and were analyzed as randomized.
Selective reporting (reporting bias)	Low risk	The trial registry record, which had been submitted before recruitment of the first participant, indicated that change in IOP was the primary and only outcome of interest. Minor differences between the trial registry record and journal publication included the addition of a follow-up time point (7 to 14 days) and subgroup analysis based on ELC time.
Other bias	Low risk	No other potential sources of bias identified.

ELC: eyelid closure; IOP: intraocular pressure.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ariturk 1996	**Not randomized:** 20 participants with POAG treated with identical antiglaucoma eye drops in both eyes; silicone punctal plugs used to occlude the inferior punctum of the eye with higher IOP, fellow eye used as control. **Not eligible intervention:** compared silicone punctal plugs with no punctal plugs.
Bartlett 1996	**Not eligible intervention:** cross-over RCT of 17 participants with POAG or ocular hypertension treated with timolol with vs without silicone punctal plugs.
Beckers 2013	**Not eligible intervention:** RCT of 805 participants with POAG or ocular hypertension treated with antiglaucoma eye drops using 1 of 4 interventions to improve adherence: use of dosing aid alone, use of dosing aid + drop guider, use of dosing aid + participant education, and use of dosing aid + drop guider + participant education.
Bohm 2014	**Not randomized:** 123 participants with POAG whose IOP was measured after topical eye drops were self-administered (day 1) and after the application of eye drops was performed by trained medical personnel (day 2).
Brinchmann-Hansen 1979	**Not eligible intervention:** cross-over RCT of 16 participants with open-angle glaucoma treated with pilocarpine eye drops vs a pilocarpine therapeutic device (Ocusert).
Brown 1984	**Not randomized:** observational study of 150 participants with glaucoma who were interviewed about how they administered their antiglaucoma eye drops and were observed as they instilled artificial tear eye drops.
De Smet 2000	**Not randomized:** literature review of how people with glaucoma apply glaucoma medications and the potential effects of these methods.
Doe 1997	**Not eligible intervention:** RCT of 23 participants treated with timolol eye drops vs timolol spray.
Flach 2008	**Not randomized:** literature review of studies that did or not use topical instillation techniques (NLO and POAG) when applying glaucoma medications.
Halberg 1975	**Not randomized:** 10 participants with open-angle glaucoma treated with pilocarpine spray in the right eye and pilocarpine eye drops in the left eye (study 1); 22 participants with open-angle glaucoma treated with pilocarpine spray only (study 2).

Study	Reason for exclusion
	Not eligible intervention: compared pilocarpine spray with pilocarpine eye drops (study 1); pilocarpine spray only (study 2).
Harris 1975	**Not randomized:** 13 participants with open-angle glaucoma treated with pilocarpine by ocular pump infusion. **Not eligible intervention:** ocular pump infusion of pilocarpine.
Huang 1989	**Not randomized:** 19 participants with open-angle glaucoma or ocular hypertension treated with identical antiglaucoma eye drops in both eyes; silicone punctal plugs used to occlude the inferior punctum of 1 eye and the fellow eye used as control; treatment assignment alternated between participants. **Not eligible intervention:** compared silicone punctal plugs with no punctal plugs.
Moolasarn 2007	**Not eligible intervention:** 340 participants with glaucoma treated at an eye clinic received an intervention program (health education) to improve adherence vs routine care.
Nordmann 2009	**Not eligible intervention:** cross-over RCT of 211 participants with POAG or ocular hypertension treated with latanoprost or fixed-combination latanoprost/timolol eyes drops instilled using a delivery device vs dropper bottle.
Okeke 2009	**Not eligible intervention:** RCT of 66 participants with glaucoma or ocular hypertension treated with antiglaucoma eye drops and receiving an intervention program to improve adherence (educational video, discussion with study coordinator, regular telephone call reminders, and audible and visible reminders using a dosing aid device) vs no intervention program.
Opitz 2011	**Not eligible intervention:** RCT of 13 participants with open-angle glaucoma or ocular hypertension treated with travoprost eye drops and receiving silicone punctal plugs in 1 eye vs no plug in the fellow eye.
Passo 1984	**Not randomized:** 10 participants with open-angle glaucoma treated with timolol eye drops (study 1); 9 participants returned for punctal occlusion following timolol instillation (study 2); 5 children with glaucoma treated with timolol eye drops tested for plasma timolol levels after instillation (study 3). **Not eligible intervention:** timolol treatment with or without punctal occlusion.
Rotberg 2006	**Not eligible intervention:** cross-over RCT of 90 participants with POAG or ocular hypertension treated with latanoprost eye drops instilled using a delivery device vs dropper bottle.
Sakiyalak 2014	**Not eligible intervention:** cross-over RCT of 59 participants with chronic glaucoma treated with eye drops instilled using a delivery device vs traditional application.
Sharir 1994	**Not eligible intervention:** a series of multiple trials aimed at evaluating short-term effects (up to 24 hours) of topically applied ocular drugs at varying doses with and without NLO. Most trials used a within-person design to compare a topical agent with placebo (NLO used for both eyes). 2 trials that used NLO in some eyes and no occlusion in others did not report methods of randomization. **Not glaucoma:** trials were performed in eyes with and eyes without glaucoma.
Sharma 2016	**Not eligible intervention:** RCT of 72 participants with POAG aimed at assessing instillation techniques when self-administering 0.5% carboxymethyl cellulose in 1 eye using a drop application strip and without the strip in the fellow eye.
Shedden 2001	**Not eligible intervention:** RCT of 286 participants with open-angle glaucoma or ocular hypertension treated with timolol eye drops vs timolol ophthalmic gel.

Study	Reason for exclusion
Simel 1988	**Not eligible intervention:** cross-over RCT of 11 participants with refractory glaucoma treated with antiglaucoma eye drops and receiving collagen lacrimal duct plugs vs no plugs.
Stewart 2002	**Not eligible intervention:** cross-over RCT of 32 participants with POAG or ocular hypertension treated with timolol ophthalmic gel prepared with xanthan gum vs gellan gum.
Urtti 1994	**Not randomized:** 12 participants with open-angle glaucoma treated with a timolol insert in 1 eye for up to 24 hours, then timolol eye drops in eyes with elevated IOP. **Not eligible intervention:** timolol insert for up to 24 hours.
Zimmerman 1984	**Not glaucoma:** 20 volunteers tested for systemic absorption of timolol eye drops after NLO for 5 minutes, no NLO, or POAG alone for 5 minutes (study 1); 16 volunteers tested for anterior chamber concentration of topical fluorescein after NLO for 5 minutes, no NLO, or POAG alone for 5 minutes (study 2).

ELC: eyelid closure; IOP: intraocular pressure; NLO: nasolacrimal; POAG: primary open-angle glaucoma; RCT: randomized controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01417689

Methods	Single-masked (outcome assessors), parallel-group randomized controlled trial Randomized by participant
Participants	Characteristics of participants unknown Target participant enrollment: 230 Inclusion criteria: • glaucoma or glaucoma suspect • use of topical glaucoma medication in both eyes for at least 1 year prior to enrollment • visual acuity of 20/60 or better with habitual correction in at least 1 eye Exclusion criteria: • previous history of allergy to fluorescein • received topical anesthesia for IOP measurement or other reason within the last 2 hours • rejects participation
Interventions	Intervention: closed eyes Participants encouraged to attempt eye drop installation with both eyes closed near the medical canthal region. After feeling contact with the drop on the skin the drop is expected to enter the eye when opening the eye and resuming blinking. Active control: open eyes Participants encouraged to attempt eye drop installation using the most commonly used technique that involves looking up, pulling inferior lid down, and putting the drop in the inferior cul de sac.
Outcomes	Primary outcome measure: complete success Complete success is defined as: participant manages to instill 1 eyedrop into the eye using only 1 eye drop. Difference in the proportion of participants achieving successful eye drop installation in each of the 2 groups. For the main analysis, the results of the first eye (right or left randomly deter-

NCT01417689 *(Continued)*

	mined will be used) a mixed model with both eyes in the analysis will also be presented for sensitivity analysis. Secondary outcome measures: qualified success, number of drops Qualified success is defined as: participant manages to instill 1 eye drop into the eye regardless of the number of drops used. Difference in the proportion of participants achieving successful eye drop installation in each of the 2 groups. For the main analysis, the results of the first eye (right or left randomly determined will be used) a mixed model with both eyes in the analysis will also be presented for sensitivity analysis. Number of drops: number of eye drops used on attempted instillation in the first eye (randomly assigned). The mean number of drops used on each of the 2 groups will be compared. Mixed models with data from both eyes will also be presented for sensitivity analysis.
Notes	Study accessed on 9 January 2017; recruitment status unknown

IOP: intraocular pressure.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01416415

Trial name or title	Glaucoma Eye Drop Installation: Impact of Education
Methods	Double-masked, parallel-group randomized controlled trial Randomized by participant
Participants	Characteristics of participants unknown Target participant enrollment: 100 Inclusion criteria: • established care with the treating ophthalmologist for ≥ 6 months • diagnosis of open-angle glaucoma or ocular hypertension • use of 1, 2, or 3 self-instilled eye drop medications in 1 or 2 eyes • age 40 to 85 years • fluency in English • best corrected visual acuity ≥ 20/50 in each eye Exclusion criteria: • presence of moderate-to-severe cognitive deficits • presence of a clinically significant tremor • Mini Mental Status Exam score ≤ 20
Interventions	Intervention: educational intervention Will contain participants who will watch a video on correct eye drop installation techniques. Control comparator: attention placebo Will contain participants who watch a video regarding healthy eating tips. The video is of similar time and attention as that shown to the intervention group.
Outcomes	Eye drop installation score (composite score of the efficacy, safety, and efficiency with which the participant instills their eyedrops) at 4 months (range 1 to 7 months)

NCT01416415 *(Continued)*

Starting date	August 2011
Contact information	Principal Investigator: Angelo Tanna Northwestern University
Notes	Study accessed on 9 January 2017; estimated completion date June 2018

NCT02697318

Trial name or title	Evaluation of a New Method for Instilling Eye Drops
Methods	Single-masked (investigator), parallel-group randomized controlled trial
Participants	Characteristics of participants unknown Target participant enrollment: 60 Aim #1 Inclusion criteria: • men and women • age 21 to 80 years • healthy volunteers with no previous history of eye disease Exclusion criteria: • no medical conditions representing contraindications to use of topical beta-blocker • no active inflammatory diseases of the eye, or diagnosis of any form of glaucoma Aim #2 Inclusion criteria: • men and women • age 21 to 80 years • diagnosed with primary open-angle glaucoma and stable on monotherapy Exclusion criteria: • no other ocular disease, or a history of prior ocular trauma, beyond minor corneal abrasion or removal of a superficial corneal foreign body
Interventions	Professional administration: Instillation of 0.5% timolol maleate (or participant's own glaucoma medication) administered by a professional, using the standard clinical method. Self-administration (new method): Instillation of 0.5% timolol maleate (or participant's own glaucoma medication) self-administered, using the new proposed method.
Outcomes	Intraocular pressure 2 hours post timolol maleate 0.5% ophthalmic solution (or participant's own glaucoma medication)
Starting date	May 2016

NCT02697318 *(Continued)*

Contact information	Contact: Michelle Steenbakkers University of Waterloo
Notes	Study accessed on 9 January 2017; estimated completion date March 2017

ADDITIONAL TABLES

Table 1. Commonly reported adverse events of medical glaucoma treatments

Drug class	Ocular adverse events	Systemic adverse events
Alpha-agonists (e.g. apraclonidine, brimonidine)	Allergic reactions Blurred vision Burning/stinging/discomfort Follicular conjunctival response Hyperemia Itching Photophobia	Allergic reactions Drowsiness Dry mouth Fatigue Headache Hypotension
Beta-blockers (e.g. betaxolol, carteolol, levobunolol, timolol)	Allergy Blurred vision Burning/stinging/discomfort Corneal erosion Dry eyes Hyperemia Hypotony Ptosis Superficial punctate keratitis Visual disturbances	Bradycardia Depression Dizziness or light-headedness Fatigue Headache Indigestion or heart pain Insomnia Joint pain Nausea Shortness of breath
Carbonic anhydrase inhibitors (e.g. acetazolamide, brinzolamide, dorzolamide)	Allergy Blurred vision Burning/stinging/discomfort Dry eyes Foreign body sensation Hyperemia Photophobia	Allergic reactions Bitter or metallic taste Dizziness Fatigue Gastrointestinal distress Headache

Table 1. Commonly reported adverse events of medical glaucoma treatments *(Continued)*

	Superficial punctate keratitis	
Parasympathomimetics (e.g. carbachol, pilocarpine)	Blurred vision	Dizziness
	Burning/stinging/discomfort	Headache
	Eyelid twitching	Hypoglycemia
	Hyperemia	Increased saliva
	Itching	Increased sweating
	Increased tearing	Nausea
	Poor vision in dim light	
	Visual disturbances	
Prostaglandin analogues (e.g. bimatoprost, latanoprost, travoprost)	Blurred vision	Cold symptoms
	Burning/stinging/discomfort	Exacerbation of asthma
	Dry eyes	Facial rash
	Eyelash growth	Joint or muscle pain
	Foreign body sensation	Upper respiratory infection
	Hyperemia	
	Increased tearing	
	Iris/skin discoloration	
	Itching	
	Photophobia	

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma] explode all trees
#2 MeSH descriptor: [Ocular Hypertension] explode all trees
#3 MeSH descriptor: [Intraocular Pressure] explode all trees
#4 glaucoma*:ti,ab,kw
#5 ((intra*ocular or ocular*) near/3 (hypertension* or tension* or pressure*)):ti,ab,kw
#6 IOP:ti,ab,kw
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Administration, Ophthalmic] explode all trees
#9 (ophthalm* near/3 (instill* or administ*)):ti,ab,kw
#10 MeSH descriptor: [Ophthalmic Solutions] this term only
#11 (eye drop* or eyedrop*):ti,ab,kw
#12 (((clos* or occlus* or occlud*) near/3 (eyelid* or duct* or lid*)) or ELC):ti,ab,kw
#13 (((nasolacrimal* or tear duct*) near/3 (occlus* or obstruct* or occlud*)) or NLO):ti,ab,kw
#14 #8 or #9 or #10 or #11 or #12 or #13
#15 MeSH descriptor: [Administration, Topical] this term only
#16 MeSH descriptor: [Instillation, Drug] explode all trees
#17 (topical* or drops*):ti,ab,kw
#18 ((drug* or medicat* or medicin*) adj3 (instill* or administ*)):ti,ab,kw
#19 (drop adj2 (instill* or administ*)):ti,ab,kw

#20 MeSH descriptor: [Prostaglandins, Synthetic] explode all trees
#21 ("Synthetic Prostaglandins" or "PG Analogs" or "Prostaglandin Analogues" or "Prostaglandin Analogs" or dimethylprostaglandin or methylprostaglandin or "prostaglandin 1"):ti,ab,kw
#22 (latanoprost* or PHXA41 or Xalatan or PhXA34 or 130209-82-4):ti,ab,kw
#23 (travoprost* or Travatan or AL-6221 or AL6221 or 157283-68-6):ti,ab,kw
#24 (bimatoprost* or latisse or Lumigan or AGN192024):ti,ab,kw
#25 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#26 ((Adrenergic near/1 beta* near/3 Blockers) or (Adrenergic near/1 beta* near/3 Blockaders) or beta* near/1 Adrenergic Blocking Agents or "Adrenergic beta Antagonists"):ti,ab,kw
#27 MeSH descriptor: [Timolol] explode all trees
#28 (Timolol* or Timoptic or Timoptol or Timacar or L-714465 or L714465 or MK-950 or MK950 or Optimol or Blocadren or 26839-75-8):ti,ab,kw
#29 MeSH descriptor: [Metipranolol] explode all trees
#30 (Metipranolol* or Methypranol or Trimepranol or Disorat or 22664-55-7):ti,ab,kw
#31 MeSH descriptor: [Carteolol] explode all trees
#32 (Carteolol* or OPC-1085 or OPC1085 or 51781-06-7):ti,ab,kw
#33 MeSH descriptor: [Levobunolol] explode all trees
#34 (Levobunolol* or PMS-Levobunolol or PMSLevobunolol or ratio-Levobunolol or Ultracortenol or Vistagan or W-6412A or W6412A or AKBeta or Apo-Levobunolol or ApoLevobunolol or Betagan or Bunolol or Novo-Levobunolol or NovoLevobunolol or W-7000A or W7000A or 47141-42-4):ti,ab,kw
#35 MeSH descriptor: [Betaxolol] explode all trees
#36 (Betaxolol* or Kerlone or Kerlon or Oxodal or SL-75212 or SL75212 or ALO-1401-02 or ALO140102 or Betoptic or Betoptima or 63659-18-7):ti,ab,kw
#37 MeSH descriptor: [Adrenergic alpha-Agonists] explode all trees
#38 ((adrenergic near/2 alpha* near/3 agonist*) or (alpha* near/2 adrenergic near/3 agent*) or (alpha* near/2 adrenergic receptor) or (alpha* near/2 adrenergic near/2 stimula*) or (alpha* near/2 adrenoceptor near/2 stimula*) or (alpha* near/3 agonist) or (alpha* sympathicomimetic) or (noradrenalin agonist*) or (noradrenergic agonist*) or (noradrenergic receptor stimulating agent*)):ti,ab,kw
#39 MeSH descriptor: [Adrenergic alpha-2 Receptor Agonists] explode all trees
#40 MeSH descriptor: [Cholinergic Agonists] explode all trees
#41 ((Acetylcholine near/2 Agonist*) or cholinergic or cholinomimetic or parasympathetic agent* or parasympathetic drug* or parasympathomimetic or parasympathomimetics):ti,ab,kw
#42 MeSH descriptor: [Carbonic Anhydrase Inhibitors] explode all trees
#43 ((Carbonic near/2 Anhydrase near/2 Inhibitor*) or (Carbonate near/2 Dehydratase near/2 Inhibitor*) or (Carboxyanhydrase near/1 Inhibitor*)):ti,ab,kw
#44 MeSH descriptor: [Acetazolamide] explode all trees
#45 (Acetazolam* or Ak-Zol or AkZol or Apo-Acetazolamide or ApoAcetazolamide or Diacarb or Diamox or Diuramide or Defiltran or Edemox or Glauconox or Glaupax or Huma-Zolamide or HumaZolamide or Acetadiazol or 59-66-5):ti,ab,kw
#46 (Brinzolamide* or Azopt or 138890-62-7):ti,ab,kw
#47 (Dorzolamide* or MK-507 or Trusopt or L-671152 or 130693-82-2):ti,ab,kw
#48 (isopropyl unoprostone* or "unoprostone isopropyl" or UF-021 or Rescula or Eescula or 69553-75-9):ti,ab,kw
#49 (brimonidine* or bromoxidine or ratio-Brimonidine or Alphagan or UK-14308 or UK-14304 or UK-14304-18 or AGN-190342 or 59803-98-4):ti,ab,kw
#50 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49
#51 MeSH descriptor: [Eye] explode all trees
#52 MeSH descriptor: [Eyelids] explode all trees
#53 MeSH descriptor: [Nasolacrimal Duct] explode all trees
#54 (ocular* or opthalm* or eye* or tear duct*):ti,ab,kw
#55 #51 or #52 or #53 or #54
#56 #50 and #55
#57 #7 and (#14 or #56)

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp glaucoma/
13. exp ocular hypertension/
14. exp intraocular pressure/
15. glaucoma*.tw.
16. ((intra*ocular or ocular*) adj3 (hypertension* or tension* or pressure*)).tw.
17. IOP.tw.
18. or/12-17
19. exp Administration, Ophthalmic/
20. (ophthalm* adj3 (instill* or administ* or solution*)).tw.
21. Ophthalmic Solutions/
22. (eye drop* or eyedrop*).tw.
23. (((clos* or occlus* or occlud*) adj3 (eyelid* or duct* or lid*)) or ELC).tw.
24. (((nasolacrimal* or 'tear duct') adj3 (occlus* or obstruct* or occlud*)) or NLO).tw.
25. or/19-24
26. Administration, Topical/
27. exp Instillation, Drug/
28. (topical* or drops).tw.
29. ((drug* or medicat* or medicin*) adj3 (instill* or administ*)).tw.
30. (Drop adj2 (instill* or administ*)).tw.
31. exp Prostaglandins, Synthetic/
32. (Synthetic Prostaglandins or PG Analogs or Prostaglandin Analogues or Prostaglandin Analogs or dimethylprostaglandin or methylprostaglandin or prostaglandin 1).tw.
33. latanoprost.rn.
34. (latanoprost* or PHXA41 or Xalatan or PhXA34 or 130209-82-4).tw.
35. travoprost.rn.
36. (travoprost* or Travatan or AL-6221 or AL6221 or 157283-68-6).tw.
37. bimatoprost.rn.
38. (bimatoprost* or latisse or Lumigan or AGN192024).tw.
39. exp Adrenergic beta-Antagonists/
40. ((Adrenergic adj1 beta* adj3 Blocker*) or (Adrenergic adj1 beta* adj3 Blockader*) or (beta* adj1 Adrenergic adj3 Blocking adj3 Agent*) or (Adrenergic adj1 beta* adj3 Antagonist*) or (beta* adj1 Adrenergic adj3 Blocking adj3 drug*) or (beta* adj2 antagonist*) or (beta* adj2 blocker*) or (beta* adj3 blocking adj2 agent*) or (beta adj3 blocking adj2 drug*) or Beta* antiadrenergic agent* or beta* sympathicolytic* or beta* sympatholytic*).tw.
41. exp timolol/
42. (Timolol* or Timoptic or Timoptol or Timacar or L-714,465 or L714465 or MK-950 or MK950 or Optimol or Blocadren or 26839-75-8).tw.
43. exp Metipranolol/
44. (Metipranolol* or Methypranol or Trimepranol or Disorat or 22664-55-7).tw.
45. exp Carteolol/
46. (Carteolol* or OPC-1085 or OPC1085 or 51781-06-7).tw.
47. exp Levobunolol/
48. (Levobunolol* or PMS-Levobunolol or PMSLevobunolol or ratio-Levobunolol or Ultracortenol or Vistagan or W-6412A or W6412A or AKBeta or Apo-Levobunolol or ApoLevobunolol or Betagan or Bunolol or Novo-Levobunolol or NovoLevobunolol or W-7000A or W7000A or 47141-42-4).tw.
49. exp Betaxolol/
50. (Betaxolol* or Kerlone or Kerlon or Oxodal or SL-75212 or SL75212 or ALO-1401-02 or ALO140102 or Betoptic or Betoptima or 63659-18-7).tw.
51. exp Adrenergic alpha-Agonists/
52. ((adrenergic adj2 alpha* adj3 agonist*) or (alpha* adj2 adrenergic adj3 agent*) or (alpha* adj2 adrenergic receptor) or (alpha* adj2 adrenergic adj2 stimula*) or (alpha* adj2 adrenoceptor adj2 stimula*) or (alpha* adj3 agonist) or alpha* sympathicomimetic or noradrenalin agonist* or noradrenergic agonist* or noradrenergic receptor stimulating agent*).tw.
53. exp Adrenergic alpha-2 Receptor Agonists/
54. exp Cholinergic Agonists/
55. ((Acetylcholine adj2 Agonist*) or cholinergic or cholinomimetic or parasympathetic agent* or parasympathetic drug* or parasympathomimetic or parasympathomimetics).tw.
56. exp Carbonic Anhydrase Inhibitors/
57. ((Carbonic adj2 Anhydrase adj2 Inhibitor*) or (Carbonate adj2 Dehydratase adj2 Inhibitor*) or (Carboxyanhydrase adj1 Inhibitor*)).tw.
58. exp Acetazolamide/
59. (Acetazolam* or Ak-Zol or AkZol or Apo-Acetazolamide or ApoAcetazolamide or Diacarb or Diamox or Diuramide or Defiltran or Edemox or Glauconox or Glaupax or Huma-Zolamide or HumaZolamide or Acetadiazol or 59-66-5).tw.

60. Brinzolamide.rn.
61. (Brinzolamide* or Azopt or 138890-62-7).tw.
62. Dorzolamide.rn.
63. (Dorzolamide* or MK-507 or Trusopt or L-671152 or 130693-82-2).tw.
64. isopropyl unoprostone.rn.
65. (isopropyl unoprostone* or unoprostone isopropyl or UF-021 or Rescula or Eescula or 69553-75-9).tw.
66. Brimonidine.rn.
67. (brimonidine* or bromoxidine or ratio-Brimonidine or Alphagan or UK-14,308 or UK-14304 or UK-14304-18 or AGN-190342 or 59803-98-4).tw.
68. or/26-67
69. exp eye/
70. exp eyelid/
71. exp Nasolacrimal Duct/
72. (ocular* or opthalm* or eye* or tear duct*).tw.
73. or/69-72
74. 68 and 73
75. 11 and 18 and (25 or 74)

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'glaucoma'/exp
#34 'intraocular hypertension'/exp
#35 glaucoma*:ab,ti
#36 ((intra*ocular OR ocular*) NEAR/3 (hypertension* OR tension* OR pressure*)):ab,ti
#37 iop:ab,ti
#38 #33 OR #34 OR #35 OR #36 OR #37
#39 'intraocular drug administration'/exp
#40 (ophthalm* NEAR/3 (instill* OR administ* OR solution*)):ab,ti

#41 'eye drops'/exp
#42 eye:ab,ti AND drop*:ab,ti OR eyedrop*:ab,ti
#43 ((clos* OR occlus* OR occlud*) NEAR/3 (eyelid* OR duct* OR lid*)):ab,ti OR elc:ab,ti
#44 ((nasolacrimal* OR 'tear duct') NEAR/3 (occlus* OR obstruct* OR occlud*)):ab,ti OR nlo:ab,ti
#45 #39 OR #40 OR #41 OR #42 OR #43 OR #44
#46 'topical drug administration'/de
#47 'drug instillation'/exp
#48 topical*:ab,ti OR drops*:ab,ti
#49 ((drug* OR medicat* OR medicin*) NEAR/3 (instill* OR administ*)):ab,ti
#50 (drop NEAR/2 (instill* OR administ*)):ab,ti
#51 'prostaglandin derivative'/exp
#52 'synthetic prostaglandins':ab,ti OR 'pg analogs':ab,ti OR 'prostaglandin analogues':ab,ti OR 'prostaglandin analogs':ab,ti OR dimethylprostaglandin:ab,ti OR methylprostaglandin:ab,ti OR 'prostaglandin 1':ab,ti
#53 'latanoprost'/exp
#54 latanoprost*:ab,ti OR phxa41:ab,ti OR xalatan:ab,ti OR phxa34:ab,ti OR '130209 82 4':ab,ti OR loutenor:ab,ti
#55 'travoprost'/exp
#56 travoprost*:ab,ti OR travatan:ab,ti OR 'al 6221':ab,ti OR al6221:ab,ti OR '157283 68 6':ab,ti OR 'fluprostenol isopropyl ester':ab,ti OR 'travatan z':ab,ti
#57 'bimatoprost'/exp
#58 bimatoprost*:ab,ti OR latisse:ab,ti OR lumigan:ab,ti OR agn192024:ab,ti OR 'agn 192024':ab,ti OR '155206 00 1':ab,ti
#59 'beta adrenergic receptor blocking agent'/exp
#60 'beta adrenergic antagonist':ab,ti OR 'beta adrenergic blocker':ab,ti OR 'beta adrenergic blockers':ab,ti OR 'beta adrenergic blocking agent':ab,ti OR 'beta adrenergic blocking drug':ab,ti OR 'beta adrenergic receptor antagonist':ab,ti OR 'beta adrenergic receptor blocker':ab,ti OR 'beta adrenoceptor antagonist':ab,ti OR 'beta adrenoceptor blocker':ab,ti OR 'beta adrenoceptor blocking agent':ab,ti OR 'beta adrenoceptor blocking drug':ab,ti OR 'beta adrenolytic':ab,ti OR 'beta adrenolytic agent':ab,ti OR 'beta antagonist':ab,ti OR 'beta antiadrenergic agent':ab,ti OR 'beta blocker':ab,ti OR 'beta blocking adrenergic agent':ab,ti OR 'beta blocking agent':ab,ti OR 'beta blocking drug':ab,ti OR 'beta receptor adrenergic blocking agent':ab,ti OR 'beta receptor blocker':ab,ti OR 'beta receptor blocking agent':ab,ti OR 'beta sympathicolytic agent':ab,ti OR 'beta sympathicolytics':ab,ti OR 'beta sympatholytic agent':ab,ti OR 'betasympatholytic agent':ab,ti
#61 'timolol'/exp
#62 timolol*:ab,ti OR timoptic:ab,ti OR timoptol:ab,ti OR timacar:ab,ti OR 'l 714465':ab,ti OR l714465:ab,ti OR 'mk 950':ab,ti OR mk950:ab,ti OR blocadren:ab,ti OR '26839 75 8':ab,ti OR 'apo timolol':ab,ti OR 'apo timol':ab,ti OR 'apo timop':ab,ti OR 'apotimol':ab,ti OR apotimolol:ab,ti OR apotimop:ab,ti OR betimol:ab,ti OR istalol:ab,ti OR moducren:ab,ti OR nyolol:ab,ti OR ofal:ab,ti OR ofan:ab,ti OR optimol:ab,ti OR timolo:ab,ti OR titol:ab,ti
#63 'metipranolol'/exp
#64 metipranolol*:ab,ti OR methypranol:ab,ti OR trimepranol:ab,ti OR disorat:ab,ti OR '22664 55 7':ab,ti OR 'beta ophtiole':ab,ti OR betalol:ab,ti OR betamann:ab,ti OR betamet:ab,ti OR betanol:ab,ti OR betanolol:ab,ti OR glauline:ab,ti OR 'normoglaucon mite':ab,ti OR ophtiole:ab,ti OR optipranolol:ab,ti
#65 'carteolol'/exp
#66 carteolol*:ab,ti OR opc1085:ab,ti OR '51781 06 7':ab,ti OR '51781 21 6':ab,ti OR arteolol:ab,ti OR arteoptic:ab,ti OR arteoptik:ab,ti OR caltamol:ab,ti OR calte:ab,ti OR carbonolol:ab,ti OR carteabak:ab,ti OR carteol:ab,ti OR cartrol:ab,ti OR 'catelon eye drop':ab,ti OR elebloc:ab,ti OR endak:ab,ti OR glauteolol:ab,ti OR karol:ab,ti OR karteol:ab,ti OR mikelan:ab,ti OR ocupress:ab,ti OR 'opc 1085':ab,ti OR stobol:ab,ti OR teoptic:ab,ti
#67 'levobunolol'/exp
#68 levobunolol*:ab,ti OR 'pms levobunolol':ab,ti OR pmslevobunolol:ab,ti OR 'ratio levobunolol':ab,ti OR ultracortenol:ab,ti OR vistagan:ab,ti OR 'w 6412a':ab,ti OR w6412a:ab,ti OR akbeta:ab,ti OR 'apo levobunolol':ab,ti OR apolevobunolol:ab,ti OR betagan:ab,ti OR bunolol:ab,ti OR 'novo levobunolol':ab,ti OR novolevobunolol:ab,ti OR w7000a:ab,ti OR '47141 42 4':ab,ti OR 'ak-beta':ab,ti OR 'ak beta':ab,ti OR betasite:ab,ti OR bunolgan:ab,ti OR gotensin:ab,ti OR 'w 7000a':ab,ti
#69 'betaxolol'/exp
#70 betaxolol*:ab,ti OR kerlone:ab,ti OR kerlon:ab,ti OR oxodal:ab,ti OR sl75212:ab,ti OR alo140102:ab,ti OR betoptic:ab,ti OR betoptima:ab,ti OR '63659 18 7':ab,ti OR 'alo 1401 02':ab,ti OR betac:ab,ti OR betarun:ab,ti OR betasel:ab,ti OR betaxon:ab,ti OR betoquin:ab,ti OR kerlong:ab,ti OR levobetaxolol:ab,ti OR lokren:ab,ti OR optibet:ab,ti OR optipress:ab,ti OR 'sl 75212':ab,ti OR tonobexol:ab,ti OR '72424 72 7':ab,ti OR '93221 48 8':ab,ti
#71 'alpha adrenergic receptor stimulating agent'/exp
#72 'adrenergic alpha-agonists':ab,ti OR 'adrenergic alpha agonists':ab,ti OR 'alpha adrenergic agent':ab,ti OR 'alpha adrenergic agonist':ab,ti OR 'alpha adrenergic receptor agent':ab,ti OR 'alpha adrenergic receptor agonist':ab,ti OR 'alpha adrenergic receptor stimulant':ab,ti OR 'alpha adrenergic receptor stimulator':ab,ti OR 'alpha adrenergic stimulant':ab,ti OR 'alpha adrenergic stimulating agent':ab,ti OR 'alpha adrenergic stimulator':ab,ti OR 'alpha adrenoceptor agonist':ab,ti OR 'alpha adrenoceptor stimulant':ab,ti OR 'alpha adrenoceptor stimulating agent':ab,ti OR 'alpha adrenoceptor stimulator':ab,ti OR 'alpha agonist':ab,ti OR 'alpha sympathicomimetic':ab,ti OR 'alpha sympathicomimetic agent':ab,ti OR 'noradrenalin agonist':ab,ti OR 'noradrenergic agonist':ab,ti OR 'noradrenergic receptor stimulating agent':ab,ti
#73 'alpha 2 adrenergic receptor stimulating agent'/exp
#74 'cholinergic receptor stimulating agent'/exp

#75 (acetylcholine NEAR/2 agonist*):ab,ti OR cholinergic:ab,ti OR cholinomimetic:ab,ti OR parasympathetic:ab,ti AND agent*:ab,ti OR parasympathetic:ab,ti AND drug:ab,ti OR parasympathetic:ab,ti AND drugs:ab,ti OR parasympathomimetic:ab,ti OR parasympathomimetics:ab,ti
#76 'carbonate dehydratase inhibitor'/exp
#77 'carboanhydrase inhibitor':ab,ti OR 'carbonic anhydrase inhibitor':ab,ti OR 'carbonate dehydratase inhibitor':ab,ti OR 'carboanhydrase inhibitors':ab,ti OR 'carbonic anhydrase inhibitors':ab,ti OR 'carbonate dehydratase inhibitors':ab,ti
#78 'acetazolamide'/exp
#79 acetazolam*:ab,ti OR 'ak zol':ab,ti OR akzol:ab,ti OR apoacetazolamide:ab,ti OR diacarb:ab,ti OR diamox:ab,ti OR diuramide:ab,ti OR edemox:ab,ti OR glauconox:ab,ti OR glaupax:ab,ti OR 'huma zolamide':ab,ti OR humazolamide:ab,ti OR '59 66 5':ab,ti OR '1424 27 7':ab,ti OR acetadiazol:ab,ti OR acetamox:ab,ti OR 'acetazol amide':ab,ti OR acetazoleamide:ab,ti OR acetozolamine:ab,ti OR albox:ab,ti OR 'apo acetazolamide':ab,ti OR azetazolamide:ab,ti OR carbinib:ab,ti OR cidamex:ab,ti OR dazamide:ab,ti OR defiltran:ab,ti OR dehydratin:ab,ti OR diluran:ab,ti OR diomax:ab,ti OR 'diuriwas wassermann barcelona':ab,ti OR diutazol:ab,ti OR eumicton:ab,ti OR fonurit:ab,ti OR genephamide:ab,ti OR glaucomed:ab,ti OR glaucomide:ab,ti OR ledamox:ab,ti OR lediamox:ab,ti OR ledimox:ab,ti OR natrionex:ab,ti OR nephramid:ab,ti OR novozolamide:ab,ti OR storzolamide:ab,ti OR ulcosilvanil:ab,ti OR ulcosylvanil:ab,ti
#80 'brinzolamide'/exp
#81 brinzolamide*:ab,ti OR azopt:ab,ti OR '138890 62 7':ab,ti OR 'al 4862':ab,ti OR al4862:ab,ti OR azoptic:ab,ti
#82 'dorzolamide'/exp
#83 dorzolamide*:ab,ti OR trusopt:ab,ti OR '130693 82 2':ab,ti OR biodrop:ab,ti OR 'l 671 152':ab,ti OR 'l 671152':ab,ti OR 'mk 13507':ab,ti OR 'mk 0507':ab,ti OR 'mk 507':ab,ti
#84 'unoprostone isopropyl ester'/exp
#85 (unoprostone NEAR/1 isopropyl*):ab,ti OR rescula:ab,ti OR eescula:ab,ti OR '69553 75 9':ab,ti OR '120373 24 2':ab,ti OR 'uf 021':ab,ti OR uf021:ab,ti
#86 'brimonidine'/exp
#87 brimonidine*:ab,ti OR bromoxidine:ab,ti OR 'ratio brimonidine':ab,ti OR alphagan:ab,ti OR 'uk 14308':ab,ti OR '59803 98 4':ab,ti OR 'agn 190342':ab,ti OR agn190342:ab,ti OR 'alphagan-p':ab,ti OR 'uk 14304':ab,ti OR 'uk 14304 18':ab,ti OR 'uk14304':ab,ti OR 'uk14304 18':ab,ti OR uk1430418:ab,ti
#88 #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87
#89 'eye'/exp
#90 'eyelid'/exp
#91 'eyelid closure'/exp
#92 'lacrimal duct'/exp
#93 ocular*:ab,ti OR opthalm*:ab,ti OR eye*:ab,ti OR (tear NEAR/1 duct*):ab,ti
#94 #89 OR #90 OR #91 OR #92 OR #93
#95 #88 AND #94
#96 #32 AND #38 AND (#45 OR #95)

Appendix 4. PubMed search strategy

#1. (glaucoma*[tiab]) NOT MEDLINE[sb]
#2. ((intraocular[tiab] OR ocular*[tiab]) AND (hypertension*[tiab] OR tension*[tiab] OR pressure*[tiab])) NOT MEDLINE[sb]
#3. (IOP[tiab]) NOT MEDLINE[sb]
#4. #1 OR #2 OR #3
#5. (ophthalm*[tiab] AND (instill*[tiab] OR administ*[tiab] OR solution*[tiab])) NOT MEDLINE[sb]
#6. (eye drop*[tiab] OR eyedrop*[tiab]) NOT MEDLINE[sb]
#7. (((clos*[tiab] OR occlus*[tiab] OR occlud*[tiab]) AND (eyelid*[tiab] OR duct*[tiab] OR lid*[tiab])) OR ELC[tiab]) NOT MEDLINE[sb]
#8. (((nasolacrimal*[tiab] OR "tear duct"[tiab]) AND (occlus*[tiab] OR obstruct*[tiab] OR occlud*[tiab])) OR NLO[tiab]) NOT MEDLINE[sb]
#9. #5 OR #6 OR #7 OR #8
#10. (topical*[tiab] OR drops[tiab]) NOT MEDLINE[sb]
#11. ((drug[tiab] OR drugs[tiab] OR medicat*[tiab] OR medicin*[tiab]) AND (instill*[tiab] OR administ*[tiab])) NOT MEDLINE[sb]
#12. (Drop[tiab] AND (instill*[tiab] OR administ*[tiab])) NOT MEDLINE[sb]
#13. ("Synthetic Prostaglandins"[tiab] OR "PG Analogs"[tiab] OR "Prostaglandin Analogues"[tiab] OR "Prostaglandin Analogs"[tiab] OR dimethylprostaglandin[tiab] OR methylprostaglandin[tiab] OR "prostaglandin 1"[tiab]) NOT MEDLINE[sb]
#14. (latanoprost*[tiab] OR PHXA41[tiab] OR Xalatan[tiab] OR PhXA34[tiab] OR 130209-82-4[tiab]) NOT MEDLINE[sb]
#15. (travoprost*[tiab] OR Travatan[tiab] OR AL-6221[tiab] OR AL6221[tiab] OR 157283-68-6[tiab]) NOT MEDLINE[sb]
#16. (bimatoprost*[tiab] OR latisse[tiab] OR Lumigan[tiab] OR AGN192024[tiab]) NOT MEDLINE[sb]
#17. ((Adrenergic[tiab] AND beta*[tiab] AND (Blocker*[tiab] OR Blockader*[tiab] OR Blocking[tiab] OR Antagonist*[tiab])) OR (beta*[tiab] AND (antagonist*[tiab] OR blocker*[tiab] OR blocking[tiab])) OR Beta* antiadrenergic agent*[tiab] OR beta* sympathicolytic*[tiab] OR beta* sympatholytic*[tiab]) NOT MEDLINE[sb]
#18. (Timolol*[tiab] OR Timoptic[tiab] OR Timoptol[tiab] OR Timacar[tiab] OR L-714,465[tiab] OR L714465[tiab] or MK-950[tiab] OR MK950[tiab] OR Optimol[tiab] OR Blocadren[tiab] OR 26839-75-8[tiab]) NOT MEDLINE[sb]

#19. (Metipranolol*[tiab] OR Methypranol[tiab] OR Trimepranol[tiab] OR Disorat[tiab] OR 22664-55-7[tiab]) NOT MEDLINE[sb]
#20. (Carteolol*[tiab] OR OPC-1085[tiab] OR OPC1085[tiab] OR 51781-06-7[tiab]) NOT MEDLINE[sb]
#21. (Levobunolol*[tiab] OR "PMS-Levobunolol"[tiab] OR PMSLevobunolol[tiab] OR "ratio-Levobunolol" OR Ultracortenol[tiab] OR Vistagan[tiab] OR W-6412A[tiab] OR W6412A[tiab] OR AKBeta[tiab] OR "Apo-Levobunolol"[tiab] OR ApoLevobunolol[tiab] OR Betagan[tiab] OR Bunolol[tiab] OR "Novo-Levobunolol"[tiab] OR NovoLevobunolol[tiab] OR W-7000A[tiab] OR W7000A[tiab] OR 47141-42-4[tiab]) NOT MEDLINE[sb]
#22. (Betaxolol*[tiab] OR Kerlone[tiab] OR Kerlon[tiab] OR Oxodal[tiab] OR SL-75212[tiab] OR SL75212[tiab] OR ALO-1401-02[tiab] OR ALO140102[tiab] OR Betoptic[tiab] OR Betoptima[tiab] OR 63659-18-7[tiab]) NOT MEDLINE[sb]
#23. ((adrenergic[tiab] AND alpha*[tiab] AND (agent*[tiab] OR receptor[tiab] OR stimula*[tiab])) OR (alpha*[tiab] AND adrenoceptor[tiab] AND stimula*[tiab]) OR (alpha*[tiab] AND agonist[tiab]) OR alpha* sympathicomimetic[tiab] OR noradrenalin agonist*[tiab] OR noradrenergic agonist*[tiab] OR noradrenergic receptor stimulating agent*[tiab]) NOT MEDLINE[sb]
#24. ((Acetylcholine[tiab] AND Agonist*[tiab]) OR cholinergic[tiab] OR cholinomimetic[tiab] OR parasympathetic agent*[tiab] OR parasympathetic drug*[tiab] OR parasympathomimetic[tiab] OR parasympathomimetics[tiab]) NOT MEDLINE[sb]
#25. ((Carbonic[tiab] AND Anhydrase[tiab] Inhibitor*[tiab]) OR (Carbonate[tiab] AND Dehydratase[tiab] AND Inhibitor*[tiab]) OR (Carboxyanhydrase[tiab] AND Inhibitor*[tiab])) NOT MEDLINE[sb]
#26. (Acetazolam*[tiab] OR Ak-Zol[tiab] OR AkZol[tiab] OR Apo-Acetazolamide[tiab] OR ApoAcetazolamide[tiab] OR Diacarb[tiab] OR Diamox[tiab] OR Diuramide[tiab] OR Defiltran[tiab] OR Edemox[tiab] OR Glauconox[tiab] OR Glaupax[tiab] OR Huma-Zolamide[tiab] OR HumaZolamide[tiab] OR Acetadiazol[tiab] OR 59-66-5[tiab]) NOT MEDLINE[sb]
#27. (Brinzolamide*[tiab] OR Azopt[tiab] OR 138890-62-7[tiab]) NOT MEDLINE[sb]
#28. (Dorzolamide*[tiab] OR MK-507[tiab] OR Trusopt[tiab] OR L-671152[tiab] OR 130693-82-2[tiab]) NOT MEDLINE[sb]
#29. (isopropyl unoprostone*[tiab] OR "unoprostone isopropyl"[tiab] OR UF-021[tiab] OR Rescula[tiab] OR Eescula[tiab] OR 69553-75-9[tiab]) NOT MEDLINE[sb]
#30. (brimonidine*[tiab] OR bromoxidine[tiab] OR ratio-Brimonidine[tiab] OR Alphagan[tiab] OR UK-14,308[tiab] OR UK-14304[tiab] OR UK-14304-18[tiab] OR AGN-190342[tiab] OR 59803-98-4[tiab]) NOT MEDLINE[sb]
#31. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#32. (ocular*[tiab] OR opthalm*[tiab] OR eye*[tiab] OR tear duct*[tiab]) NOT MEDLINE[sb]
#33. #31 AND #32
#34. #4 AND (#9 OR #33)
#35. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#36. #34 AND #35

Appendix 5. LILACS search strategy

(Glaucoma$ OR MH:C11.525.381$ OR "Ocular Hypertension" OR "Hipertensión Ocular" OR "Hipertensão Ocular" OR MH:C11.525$ OR "Intraocular Pressure" OR "Presión Intraocular" OR "Pressão Intra-Ocular" OR MH:G14.440$ OR IOP OR "intraocular hypertension" OR "intraocular tension" OR "intraocular pressure" OR "ocular tension" OR "ocular pressure") AND (("Ophthalmic Administration" OR "Administración Oftálmica" OR "Administração Oftálmica" OR "Ocular Administration" OR MH:E02.319.267.120.805$ OR ((ophthalm $) AND (instill$ OR administ$ OR solution$)) OR "Ophthalmic Solutions" OR "Soluciones Oftálmicas" OR "Soluções Oftálmicas" OR MH:D26.255.775.645$ OR eyedrop$ OR eyedrop OR "eye drop" OR "eye drops" OR ((clos$ OR occulus$ OR occlude$) AND (eyelid$ OR duct$ OR lid$ OR nasolacrimal$)) OR ELC OR NLO) OR ((Topical$ OR Tópica$ OR drops OR MH:E02.319.267.120$ OR "Drug Instillation" OR "Instilación de Medicamentos" OR "Instilação de Medicamentos" OR MH:E02.319.267.641$ OR ((drug$ OR medicat$ OR medicin$ OR drop) AND (instill$ OR administ$)) OR "Synthetic Prostaglandins" OR "Prostaglandinas Sintéticas" OR MH:D10.251.355.255.550.700$ OR "PG Analogs" OR "Prostaglandin Analogues" OR "Prostaglandin Analogs" OR latanoprost$ OR Xalatan OR Travoprost$ OR Travatan OR bimatoprost$ OR Lumigan OR "Adrenergic beta Antagonists" OR "Antagonistas Adrenérgicos beta" OR "beta Adrenergic Receptor Blockader" OR "beta Adrenergic Blocking Agent" OR MH:D27.505.519.625.050.200.200$ OR Timolol$ OR MH:D02.033.100.624.915$ OR Timoptic OR Timoptol OR Metipranolol$ OR Trimepranol OR MH:D02.033.100.624.545$ OR Carteolol$ OR MH:D02.033.100.624.210$ OR Levobunolol$ OR Bunolol OR MH:D02.033.100.624.500$ OR Betaxolol$ OR Betoptic OR MH: D02.033.100.624.102$ OR "Adrenergic alpha Agonists" OR "alpha Adrenergic Receptor Agonists" OR "Adrenergic alpha Receptor Agonists" OR MH:D27.505.519.625.050.100.100$ OR "Adrenergic alpha 2 Receptor Agonists" OR "Agonistas de Receptores Adrenérgicos alfa 2" OR MH:D27.505.519.625.050.100.100.200$ OR "Cholinergic Agonists" OR "Agonistas Colinérgicos" OR "Acetylcholine Agonists" OR MH: D27.505.519.625.120.140$ OR "Carbonic Anhydrase Inhibitors" OR "Inhibidores de Anhidrasa Carbónica" OR "Inibidores da Anidrase Carbônica" OR "Carbonate Dehydratase Inhibitors" OR MH:D27.505.519.389.200$ OR Acetazolam$ OR Diamox OR MH: D02.886.675.867.060$ OR Brinzolamide$ OR Dorzolamide$ OR Trusopt OR isopropyl unoprostone$ OR Rescula OR brimonidine$ OR Alphagan) AND (eye OR Ojo OR Olho OR MH:A01.456.505.420$ OR eyelids OR Párpados OR Pálpebras OR MH:A01.456.505.420.504$ OR "Nasolacrimal Duct" OR "Conducto Nasolagrimal" OR "Ducto Nasolacrimal" OR MH:A09.371.463.640$ OR ocular$ OR opthalm$ OR eye$ OR tear duct$)))

Appendix 6. International Pharmaceutical Abstracts search strategy

S1 glaucoma*
S2 ((intra#ocular OR ocular*) AND (hypertension* OR tension* OR pressure*))
S3 IOP

S4 S1 OR S2 OR S3
S5 (ophthalm* AND (instill* OR administ* OR solution*))
S6 (eye drop* OR eyedrop*)
S7 (((clos* OR occlus* OR occlud*) AND (eyelid* OR duct* OR lid*)) OR ELC)
S8 (((nasolacrimal* OR 'tear duct') AND (occlus* OR obstruct* OR occlud*)) OR NLO)
S9 S5 OR S6 OR S7 OR S8
S10 topical* OR drops
S11 ((drug* OR medicat* OR medicin*) AND (instill* OR administ*))
S12 (Drop AND (instill* OR administ*))
S13 ("Synthetic Prostaglandins" OR "PG Analogs" OR "Prostaglandin Analogues" OR "Prostaglandin Analogs" OR dimethylprostaglandin OR methylprostaglandin OR "prostaglandin 1")
S14 (latanoprost* OR PHXA41 OR Xalatan OR PhXA34 OR 130209-82-4)
S15 (travoprost* OR Travatan OR AL-6221 OR AL6221 OR 157283-68-6)
S16 (bimatoprost* OR latisse OR Lumigan OR AGN192024)
S17 ((Adrenergic N1 beta* AND Blocker*) OR (Adrenergic AND beta* AND Blockader*) OR (beta* AND Adrenergic AND Blocking AND Agent*) OR (Adrenergic AND beta* AND Antagonist*) OR (beta* AND Adrenergic AND Blocking AND drug*) OR (beta* AND antagonist*) OR (beta* AND blocker*) OR (beta* AND blocking AND agent*) OR (beta AND blocking AND drug*) OR Beta* antiadrenergic agent* OR beta* sympathicolytic* OR beta* sympatholytic*)
S18 (Timolol* OR Timoptic OR Timoptol OR Timacar OR L-714,465 OR L714465 OR MK-950 OR MK950 OR Optimol OR Blocadren OR 26839-75-8)
S19 (Metipranolol* or Methypranol or Trimepranol or Disorat or 22664-55-7)
S20 (Carteolol* or OPC-1085 or OPC1085 or 51781-06-7)
S21 (Levobunolol* or PMS-Levobunolol or PMSLevobunolol or ratio-Levobunolol or Ultracortenol or Vistagan or W-6412A or W6412A or AKBeta or Apo-Levobunolol or ApoLevobunolol or Betagan or Bunolol or Novo-Levobunolol or NovoLevobunolol or W-7000A or W7000A or 47141-42-4)
S22 (Betaxolol* or Kerlone or Kerlon or Oxodal or SL-75212 or SL75212 or ALO-1401-02 or ALO140102 or Betoptic or Betoptima or 63659-18-7)
S23 ((adrenergic N2 alpha* N3 agonist*) or (alpha* N2 adrenergic N3 agent*) or (alpha* N2 adrenergic receptor) or (alpha* N2 adrenergic N2 stimula*) or (alpha* N2 adrenoceptor N2 stimula*) or (alpha* N3 agonist) or alpha* sympathicomimetic or noradrenalin agonist* or noradrenergic agonist* or noradrenergic receptor stimulating agent*)
S24 ((Acetylcholine N2 Agonist*) or cholinergic or cholinomimetic or parasympathetic agent* or parasympathetic drug* or parasympathomimetic or parasympathomimetics)
S25 ((Carbonic N2 Anhydrase N2 Inhibitor*) or (Carbonate N2 Dehydratase N2 Inhibitor*) or (Carboxyanhydrase N1 Inhibitor*))
S26 (Acetazolam* or Ak-Zol or AkZol or Apo-Acetazolamide or ApoAcetazolamide or Diacarb or Diamox or Diuramide or Defiltran or Edemox or Glauconox or Glaupax or Huma-Zolamide or HumaZolamide or Acetadiazol or 59-66-5)
S27 (Brinzolamide* or Azopt or 138890-62-7)
S28 (Dorzolamide* or MK-507 or Trusopt or L-671152 or 130693-82-2)
S29 (isopropyl unoprostone* or "unoprostone isopropy"l or UF-021 or Rescula or Eescula or 69553-75-9)
S30 (brimonidine* or bromoxidine or ratio-Brimonidine or Alphagan or UK-14,308 or UK-14304 or UK-14304-18 or AGN-190342 or 59803-98-4)
S31 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
S32 (ocular* or opthalm* or eye* or eyelid or tear duct* or "nasolacrimal duct")
S33 S31 AND S32
S34 S4 AND (S9 OR S33)

Appendix 7. *meta*Register of Controlled Trials search strategy

(Glaucoma OR glaucomas OR "ocular hypertension") AND ("Ophthalmic solution" OR Instillation OR Topical OR Topically OR "eyelid closure" OR "eye lid closure" OR "nasolacrimal occlusion" OR eyedrop OR eyedrops OR drops)

Appendix 8. ClinicalTrials.gov search strategy

(condition) Glaucoma OR glaucomas OR "ocular hypertension"

(intervention) "Ophthalmic solution" OR Instillation OR Topical OR Topically OR "eyelid closure" OR "eye lid closure" OR "nasolacrimal occlusion" OR eyedrop OR eyedrops OR drops

Appendix 9. ICTRP search strategy

(condition) Glaucoma OR glaucomas OR ocular hypertension

(intervention) Ophthalmic solution OR Instillation OR Topical OR Topically OR eyelid closure OR eyedrop OR eyedrops

CONTRIBUTIONS OF AUTHORS

- LX developed, designed, and wrote the protocol. XW and MW provided feedback on the protocol.
- Conceiving and designing the review: LX.
- Designing and undertaking search strategies: Lori Rosman (Cochrane Eyes and Vision (CEV)).
- Screening search results: LX, XW, MW, CEV.
- Organizing retrieval of papers: LX.
- Screening retrieved papers against inclusion criteria: LX, XW, MW.
- Appraising risk of bias: LX, XW, MW, CEV.
- Extracting data from papers: LX, XW, MW.
- Writing to authors of papers for additional information: LX.
- Entering data into Review Manager 5: LX, XW, MW.
- Analysis of data: LX, XW, MW.
- Interpretation of data:
  - providing a methodological perspective: LX, XW, MW, CEV;
  - providing a clinical perspective: LX, XW, MW;
  - providing a consumer perspective: LX, XW, MW.
- Writing the review: LX, XW, MW.

DECLARATIONS OF INTEREST

LX: none known.
XW: none known.
MW: none known.

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The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the assessment of the certainty of evidence using the GRADE approach and a 'Summary of findings' table to the review methods. The 'Summary of findings' table was not part of the original Cochrane protocol, thus the selection of outcomes presented in the table was made post hoc. We based our selection on core outcomes for glaucoma research that have been proposed in the literature (Ismail 2016).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Ophthalmic; Antihypertensive Agents [*administration & dosage] [adverse effects]; Bimatoprost [administration & dosage]; Eyelashes [anatomy & histology] [drug effects]; Glaucoma [*drug therapy]; Intraocular Pressure [*drug effects]; Latanoprost; Ophthalmic Solutions [administration & dosage] [adverse effects]; Prostaglandins F, Synthetic [administration & dosage]; Randomized Controlled Trials as Topic; Travoprost [administration & dosage]

MeSH check words

Humans